Harvard Medicine

SPRING 2011

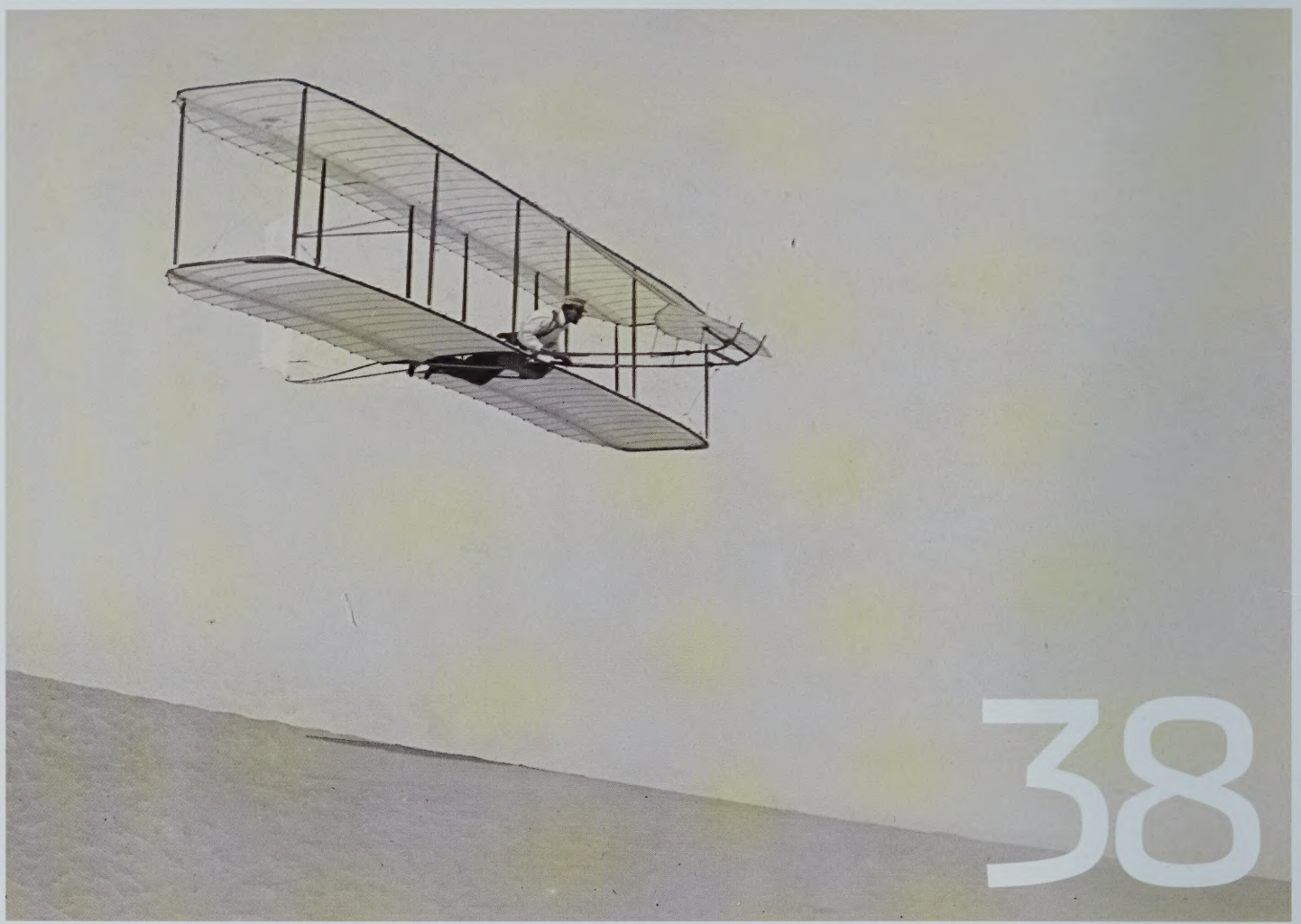


Impossible Medicine

Why Harvard doctors are undaunted by the demands of discovery

CONTENTS

SPRING 2011 | VOLUME 84 | NUMBER 1



38



8

Departments

2 From the Dean

3 Letters to the Editor

4 Pulse

A focus on primary care; diabetes research innovations; the role of physicians in perpetrating Holocaust horrors

7 Benchmarks

Diagnosing diabetes and autism early; preventing Parkinson's and infertility

44 Assembly Instructions

How to Build a Better Health Care Delivery Model
by Jessica Cerretani

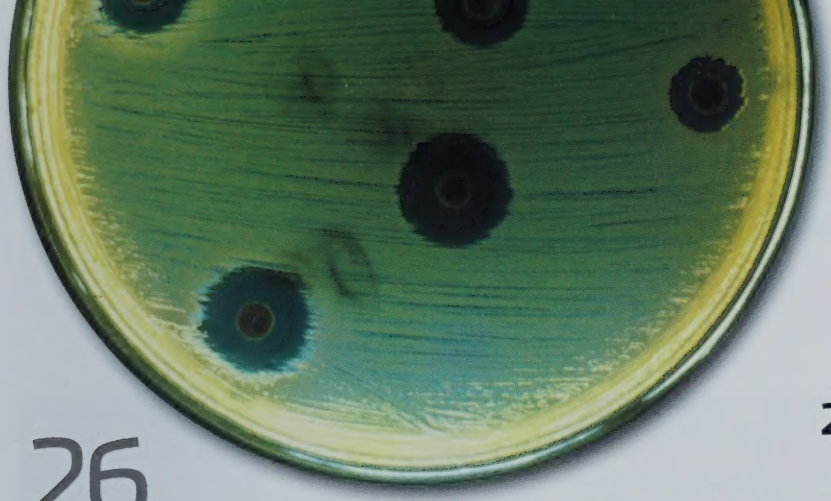
46 Smart Science

Fancy Footwork
by R. Alan Leo

48 Five Questions

Sanjiv Chopra on Medical Myths
interview by Jessica Cerretani

COVER PHOTO: ANN CUTTING



26

Special Report:
Impossible Medicine

12 The Discovery Channel
Why do Harvard doctors remain undaunted by the demands of discovery?
by Cathryn Delude

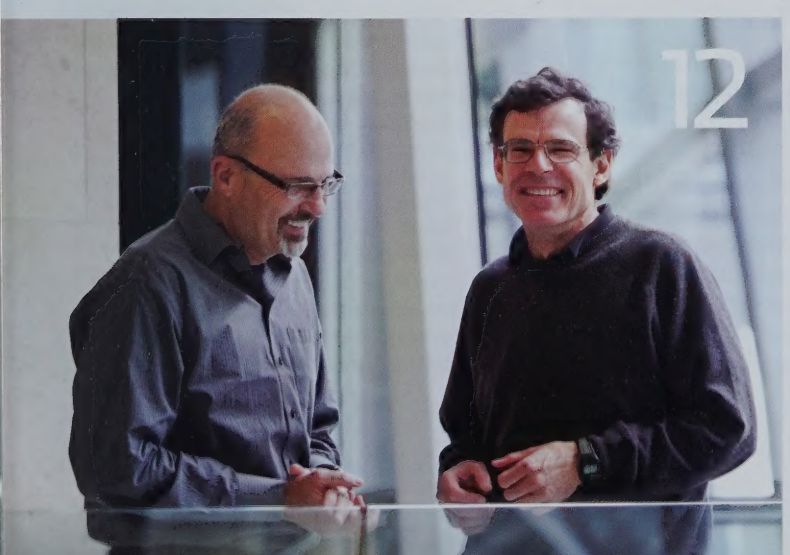
20 Anatomy of a Discovery
This story ends happily, if not where anyone expected, in a lifesaving treatment for cancer.
by Elizabeth Dougherty

22 This Glorious Quest
Harvard Medical School's executive dean for research offers a vision for partnerships that move discoveries from bench to bedside.
interview by David Cameron

26 The Twilight Zone
What discoveries were unimaginable even a decade ago?
by Ann Marie Menting

32 Trading Spaces
Leaders in medical research can enrich their creative output by moving between industry and academia.
by Jessica Cerretani and R. Alan Leo

38 They All Laughed
Harvard doctors have a long tradition of earning the last laugh by persevering in the face of skepticism.
by Jessica Cerretani





From the Dean

THOUGHTS ON INNOVATION



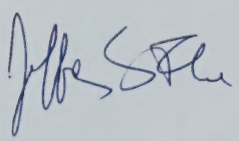
More than three decades ago, while fresh from my clinical residency, I took a mentor's advice and joined a laboratory engaged in exciting research in diabetes. Sadly, my ambition outpaced my skills, and after repeated experimental failures, I vowed to abandon bench research. But one night, as I watched data emerging from a gamma counter, I realized that my results looked promising. I still remember that extraordinary feeling: in the hush of the laboratory, I suddenly understood a disease mechanism that no one before me had grasped. The thrill of discovery has since fueled my career—and my passion for leading this School.

The quest for discovery drives much of the work we do at HMS and its affiliated institutions. Yet the odds against laboratory results reaching patients often seem insurmountable. False paths greatly outnumber true ones. Only one drug among more than a hundred promising candidates succeeds. And the constraints on our ability to translate laboratory discoveries into safe, effective, and approved therapeutics are severe, including shrinking resources, limitations in animal models and technologies, and a labyrinth of regulations.

By many measures, medicine *should* be impossible. Yet, I'm proud to note, this community of faculty—along with the wealth of intellectual capital we find in our trainees, our students, and our alumni, near and far—share a determination to overcome the obstacles to translating discoveries from laboratory bench to bedside.

In fact, the productivity of the HMS community astounds me. Faculty members lead a range of investigations, from the most basic, to the translational and the clinical, to social science, policy, and global health. Research funding at the School and its affiliates exceeds $1.5 billion annually, and each year HMS researchers publish thousands of findings in scientific journals.

These scientists join a centuries-long lineage of HMS investigators who have withstood serial failures, rebuffed conventional wisdom, and infused our collective knowledge with fresh insight. This issue of *Harvard Medicine* traces their paths to discovery, marked with serendipity and significance, agility and innovation, singleness of purpose and downright obstinacy.



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Letters to the Editor

SECOND OPINIONS FROM OUR READERS



Dilemmas of Destiny

Many of us in the medical field worry about the implications of preimplantation genetics. In the short term, such genetic selection can fuel social discrimination.

ANTHONY PATTON '58
DANVERS, MASSACHUSETTS

Designer Genes

I found "Dilemmas of Destiny," Ann Marie Menting's article on the ethical implications of personalized medicine, to be well crafted. The author explored with great sensitivity the delicate matter of sharing information about the very personal nature of one's genetic makeup.

Many of us in the medical field worry especially about the implications of preimplantation genetics. Our concern is not so much about testing for and acting to change the genetic underpinnings of a disease that causes individual suffering and devastation. Relieving suffering, after all, is what doctors do. But altering or selecting for genes that produce traits that someone has decided are good or confer some benefit in terms of class, beauty, or economic or intellectual benefit—that is deeply troubling.

In the short term, such genetic selection can fuel social discrimination and lead to such horrors as eugenics and genocide. In the long term, selecting for traits that are "fashionable" could even jeopardize our species. We don't fully understand why evolution has produced the diversity it has among humans. We're still scratching the surface of understanding, and we have a long way to go before we'll fully understand all gene–gene interactions or how those interactions help determine our survival. Prudence should prevail as we explore the medical benefits of preimplantation genetics, but changing genetic outcomes to satisfy the whims of society? We must avoid that at all costs.

ANTHONY PATTON '58
DANVERS, MASSACHUSETTS

The Lending Spree

I just wanted to let you know that I used to give away my copies of your magazine in the old format, the *Harvard Medical Alumni Bulletin*, unread. I will still loan it out to friends, but if future issues are anything like the one on personalized medicine, you can bet I will have read it first. I think you've unlocked the secret of exposing the fascinating science that's done at Harvard without making it seem like you're just name-dropping the latest guy (and occasional gal) who won a big grant. Thank you!

ROY AUTY, PHD
BROOKLYN, NEW YORK

A Way with Words

The new format and expanded range of topics found in the new *Harvard Medicine* is certainly impressive and appropriate for the times. While I always enjoyed receiving the *Harvard Medical Alumni Bulletin*, Harvard Medical School and its famous affiliates have grown and so have you. I appreciate the thoughtful and authoritative articles and the attractive photos and illustrations that accompany the discourse in the fields of medicine, medical education, and medical politics. I think you have produced a winner.

ARMAND LEFEMINE '52
CENTERVILLE, MASSACHUSETTS

*Harvard Medicine welcomes letters to the editor. Please send letters by mail (*Harvard Medicine, *25 Shattuck Street, Boston, Massachusetts 02115); fax (617-432-0089); or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length or clarity. The magazine also welcomes ongoing feedback through its Readers' Panel. To become a member, visit harvardmedicine.hms.harvard.edu/feedback.php.*



Magazine Honors

At the 2010 Eddie and Ozzie Awards ceremony held in New York City this past January, *Harvard Medicine* received three awards in the association/nonprofit category—a gold medal for best full issue, a silver for best redesign, and a bronze for best website.



HANDLING WITH CARE: Brittany Dixon, a third-year HMS student, participates in the Crimson Care Collaborative, a student-designed initiative at Massachusetts General Hospital that seeks to expand patients' access to primary care. The same zeal for solving the country's primary care crisis led to the School's new Center for Primary Care.

CENTERING ON PRIMARY CARE

An ambitious initiative seeks to remedy a national crisis

HARVARD MEDICAL SCHOOL'S nascent Center for Primary Care, announced last fall, has as its mission nothing short of transforming primary care.

"This new center will more effectively position HMS to develop programs and train leaders in primary care and health systems research, education, and policy," says Jeffrey Flier, dean of HMS. "The center will also contribute to innovation in primary care delivery, which we expect to have transformative, global impact." Made possible by a $30-million anonymous gift, the center will have physical and virtual dimensions, serving as both an actual and intellectual docking point for students, residents, fellows, and faculty from across the School and its affiliated hospitals.

Over the past several years, Flier says, stakeholders nationwide have acknowledged a primary care crisis in the United States. Despite mounting evidence that health care systems with a primary care orientation provide better care at lower cost, primary care receives less funding in the United States in proportion to specialized disciplines than in any other developed nation. Primary care providers are typically underpaid and overworked compared with other medical specialists, and many of them feel disillusioned. Fewer students are choosing to practice primary care, and many primary care physicians are opting out of the system through early retirement or other career changes. In the face of this dire picture, groups around the country are innovating primary care delivery models that better serve patients and physicians alike and offer the potential to help change the health care delivery system.

The School's Center for Primary Care grew out of a yearlong collaborative effort led by the Primary Care Advisory Group, made up of HMS faculty, students, administrators, and residents. A second group, Primary Care Progress, organized a series of town hall–style meetings that brought together hundreds of members of the Harvard primary care community to contribute to the dialogue. The new center will draw together HMS students, basic science and clinical faculty, experts from other Harvard schools, and an extensive network of national and international collaborators, and provide them with financial resources to tackle three broad areas: primary care education; local, national, and international leadership in primary care; and primary care delivery and innovation research.

"The center's establishment speaks to the dedication and vision of the HMS community," says Flier. "It is at moments like these that I'm especially proud to be here."

—David Cameron

PHOTOS: JOSHUA TOUSTER (LEFT); JUSTIN IDE/HARVARD NEWS OFFICE (RIGHT); STEPHANIE MITCHELL/HARVARD NEWS OFFICE (FAR RIGHT)





BRIDGE TEAM: Douglas Melton (left), the Thomas Dudley Cabot Professor in the Natural Sciences at Harvard, and Richard Lee, an HMS professor of medicine at Brigham and Women's Hospital, are collaborating to engineer cells that monitor blood glucose in people with diabetes.

The Magnificent Seven

New projects offer innovative approaches to diabetes

SEVEN RESEARCH TEAMS with fresh approaches to solving the riddle of type 1 diabetes have received funding through an initiative that first tapped the creativity of Harvard community members just over a year ago.

In February 2010 the Harvard Clinical and Translational Science Center, known as Harvard Catalyst, launched a crowdsourcing experiment called the Ideation Challenge. Some 40,000 faculty, staff, and students, along with the general public, were invited to answer a simple question: What do we not know to cure type 1 diabetes?

A panel of experts reviewed 190 suggestions and zeroed in on a dozen outstanding responses—some of them from nonexperts, including a Harvard College student and an HMS human resources manager. Contest winners each received $2,500 and agreed to release their ideas and intellectual property to Harvard.

In November, the Harvard Institute of Translational Immunology, or HITI, solicited proposals for research to explore several of the winning ideas. From a pool of 31 entries, seven were deemed most worthy of funding. The pilot grant program, supported with $1 million from the Leona M. and Harry B. Helmsley Charitable Trust, is HITI's first effort to convene multidisciplinary translational and clinical investigators from across Harvard to study immune-mediated diseases.

According to HITI's codirectors, Arlene Sharpe '82, the George Fabyan Professor of Comparative Pathology at HMS, and Laurence Turka, an HMS lecturer on medicine at Beth Israel Deaconess Medical Center, the goal of these seven projects is threefold: to better understand the origins of immune-mediated diseases; to formulate immune-based assays to support human clinical trials and improve diagnostics; and, ultimately, to develop novel therapies.

Most of the winning entries involve the creation of new multidisciplinary teams that introduce investigators to the study of type 1 diabetes. The pilot projects will seek to: test the therapeutic potential of populations of a particular immune cell; synthetically produce small sets of proteins to measure whether they might be recognized by antibodies in people with diabetes; identify genetic biomarkers that may predict the disease before its onset; employ nanomaterials in ways that help the immune system inhibit the development of insulin-producing cells; engineer cells to act as blood glucose monitors; use molecular biology and microfabrication techniques to build highly sensitive, autoantibody-detection devices; and develop ways to convert specific cells in the pancreas into fully functioning, insulin-releasing cells to replace destroyed cells.

Speeding the Path to Professorship

THE AVERAGE TIME FOR PROMOTION to professor is expected to drop sharply at Harvard Medical School under a new, streamlined process that Dean Jeffrey Flier announced in February.

Under the revised process, most professorial promotions should take less than one year from initiation to final decision. This expedited process consolidates many steps that formerly took place at the hospitals and at HMS into a single, more efficient model. The number of steps will be halved under the new approach.

"The changes to our promotion process," says Flier, "will allow Harvard Medical School to reward our most outstanding faculty with timely recognition of their accomplishments without compromising the thoroughness and rigor of the evaluation."

Research Rewarded

JEFFREY FLIER, DEAN OF HMS, recently received the international 2010 Rolf Luft Award from the Karolinska Institute in Sweden for seminal contributions to the understanding of the physiology of insulin and leptin and the mechanisms underlying their defective action in metabolic diseases.

Flier's contributions to the understanding of obesity and insulin resistance have had a significant impact on lipid research, particularly in the arena of leptin action and resistance. He is credited with the groundbreaking observation that leptin is likely to be the key signal that informs the brain of the transition between the adequately nourished and the starved state. Flier has also made substantive contributions to research on the metabolic syndrome as well as on insulin action and resistance.



TROUBLING SCIENCE: Even before the Nazi era, German medical science was preoccupied with heredity. In this 1920s photo, a physician examines twins as part of a study to determine whether undesirable conditions are inherited and thus might be stemmed by state-sanctioned sterilization.

Deadly Medicine

An exhibit explores eugenics in the Nazi Era

PHYSICIANS PLEDGE TO DO NO HARM, yet many participated in the genocide promulgated in Nazi Germany. How could they have collaborated with government leaders to sterilize and kill "undesirables" during the Nazi era? What were the intertwined ideological and scientific origins of "racial hygiene"? And what lessons might we draw for contemporary medicine and society?

An exhibit titled *Deadly Medicine: Creating the Master Race* is encouraging the Harvard Medical School community to spark discussions on these and other questions. Produced by the United States Holocaust Memorial Museum, the exhibition will be ongoing at the Countway Library of Medicine through July 17. This Boston venue, together with the range of public programs scheduled to accompany it, is a joint effort of the museum and the School.

The exhibit presents long-hidden documents, rarely seen photographs, and historical film footage to illustrate the role that physicians, public health officials, scientists, and academics played in implementing the Nazis' program of racial hygiene. By tracing the development of ideas about eugenics, the exhibit examines how the goal of human perfection led to the horror that was the Holocaust.

"*Deadly Medicine* challenges our community to be reflective about the profession of medicine and the actions of its practitioners," says Scott Podolsky '97, director of the Countway's Center for the History of Medicine and an HMS assistant professor of global health and social medicine. "First, medicine and medical science are never truly value free; they are always embedded in the values of the society. Second, this exhibit reminds us of our primary obligation to our patients, rather than to any larger entity."

To view an online exhibit and to learn about related events, visit www.ushmm.org/museum/exhibit/online/deadlymedicine.

—Ann Marie Menting

Building the Best Team Possible

FOLLOWING A YEAR of rigorous discussion, the Harvard Medical School Task Force on Faculty Development and Diversity has completed its charge of developing comprehensive recommendations aimed at creating an even more vibrant and diverse faculty and trainee community. Jeffrey Flier, dean of HMS, asked the group to develop recommendations in 2009, convening more than 60 faculty and staff members from throughout HMS and its affiliated hospitals. Flier has now accepted all of the group's recommendations.

"Harvard Medical School has long supported faculty development and diversity through a variety of successful programs and initiatives because we are deeply committed to the careers of all our faculty members, junior and senior alike," says Flier. "I am personally committed to ensuring that we do all that we can to help our faculty members advance professionally. This task force has shown us how to continue building an even more inclusive and welcoming community across all ranks and disciplines, especially for women and underrepresented minorities. For this reason I welcome and embrace these recommendations."

The recommendations include: establishing programs to help new and existing faculty members advance their careers and feel more connected to the HMS community; developing an expansive communications outreach effort to promote the values, goals, and programs of faculty development and diversity at HMS; streamlining the faculty promotions process; and improving search practices to help broaden recruitment efforts and create a more diverse faculty community.

"Diversity and excellence go hand in hand," says Flier. "Diversity is a prerequisite for world leadership and essential for transforming culture."

For more information, visit http://aca.hms.harvard.edu/?p=65.

PHOTOS: ARCHIV ZUR GESCHICHTE DER MAX-PLANCK-GESELLSCHAFT, BERLIN-DAHLEM (LEFT); JOHN SOARES (ABOVE RIGHT); KRIS SNIBBE/HARVARD NEWS OFFICE (RIGHT)



ALL IN PERSPECTIVE: Neurobiologist Margaret Livingstone and colleagues have found that a flaw in stereoscopic vision may help artists collapse three dimensions to two on canvas.

THE EYES HAVE IT

Poor stereopsis may aid artists

One of the challenges of learning to paint the world is figuring out how to collapse the three dimensions of life onto a two-dimensional canvas. Part of that difficulty is technical; the evolving artist must grasp the subtleties of paint, stroke, and composition in order to depict depth and space. Another hurdle is neurological; the artist must figure out how to undermine the stereoscopic accuracy of binocular vision. In short, the artist must learn to "see" three dimensions as two before he or she can render well real-world perspective.

Or perhaps, if you're Edward Hopper, say, or Marc Chagall, Alexander Calder, or Pablo Picasso, you might rely on a natural aberration: a deficit in your stereoscopic vision.

Writing in the March issue of *Psychological Science*, Margaret Livingstone, an HMS professor of neurobiology, and colleagues report that difficulties with stereopsis, the perception of depth generated by the brain from the sensory input of both eyes, are more common among artists than non-artists. Moreover, according to the team's assessment of photographs of established artists, artists' eyes often show misalignment, especially when compared to a control population of non-artists. Eye misalignment, a condition known as strabismus, contributes to poor stereopsis.

The unexpected advantage gained by overriding the brain's tendency to layer depth into the tandem views captured by the eyes has long been recognized by teachers of art. Budding representational artists are often counseled to close one lid and peer through a single eye at the subject of their attention. Shutting one eye, says Livingstone, defeats stereopsis and heightens visual cues for depth, such as shading and perspective.

In a two-part study, Livingstone—along with Bevil Conway, an HMS lecturer on neurobiology, and former Wellesley student Rosa Lafer-Sousa—tested stereoscopic accuracy among 403 art students from two U.S. art schools noted for their emphasis on representational rendering. The researchers then compared those results with the same measurements for 190 nonartist peers at two universities. Next, the investigators assessed stereopsis among established artists by adapting an eye-alignment test and using it to measure alignment in photographed eyes. As a control, the team measured eye alignment in photographs of an age- and gender-matched group of U.S. congressional representatives.

The team found not only poorer stereoscopic accuracy among the art students than among the nonartists, but also a prevalence of eye misalignment among the established artists, indicating an increased incidence of strabismus.

Does all this mean poor eye alignment is necessary for artistic success? No, cautions Livingstone: "You can get the same effect simply by closing one eye. But, at a minimum, if poor stereopsis doesn't contribute to artistic talent, it certainly doesn't detract from it."

—*Ann Marie Menting*

A Protective Effect

ADULTS WHO REGULARLY TAKE IBUPROFEN, a nonsteroidal anti-inflammatory drug, or NSAID, have about one-third less risk of developing Parkinson's disease than nonusers, a recent Harvard study found.

"There is no cure for Parkinson's disease, so the possibility that ibuprofen, an existing and relatively nontoxic drug, could help protect against the disease is captivating," says Alberto Ascherio, an HMS professor of medicine at Brigham and Women's Hospital and the senior author of the report in the March 8 issue of *Neurology*.

Parkinson's, a progressive nervous system disease, affects at least half a million people in the United States alone. It has been suggested that ibuprofen may reduce brain inflammation that may contribute to the disease.

Using data from more than 135,000 participants enrolled in two long-term studies, the team identified 291 cases (156 men and 135 women) of Parkinson's disease and analyzed the questionnaire responses of these participants to determine use of analgesics.

The scientists found that those who used ibuprofen two or more times per week were about 38 percent less likely to develop Parkinson's disease than those who regularly used aspirin, other NSAIDs, or similar agents, such as Tylenol.



CALMING AGENT: Ibuprofen, whose molecular structure is modeled here, is an anti-inflammatory agent that may help prevent Parkinson's disease.



SHAM SUCCESS: Ted Kaptchuk and colleagues found placebos to be powerful even when test subjects knew they were taking only sugar pills.

When First We Practice to Deceive

With placebos, it's all in your head—and that's okay

FOR MOST OF US, the "placebo effect" is synonymous with the power of positive thinking; it works because you believe you're taking a real drug. But Harvard researchers are now rattling this assumption.

Researchers at the School's Osher Research Center and Beth Israel Deaconess Medical Center (BIDMC) have found that placebos work even when administered without the seemingly requisite deception. The study appeared in the December 22 issue of *PLoS ONE*.

Data on the placebo effect are so compelling that many U.S. physicians—one study estimates 50 percent—secretly give dummy pills to unsuspecting patients. The ethically questionable nature of such a practice led Ted Kaptchuk, an HMS associate professor of medicine, to team up with BIDMC colleagues to explore whether the power of placebos can be harnessed honestly and respectfully.

The researchers divided 80 patients suffering from irritable bowel syndrome (IBS) into two groups: the control group, which received no treatment, and the test group, which received a regimen of placebos—disclosed as "like sugar pills"—which they were instructed to take twice daily.

"Not only did we make it absolutely clear that these pills had no active ingredient and were made from inert substances, but we actually had 'placebo' printed on the bottle," says Kaptchuk. "We told the patients that they didn't even have to believe in the placebo effect. Just take the pills."

For a three-week period, the patients were monitored. By the end of the trial, nearly twice as many patients treated with the placebo reported adequate symptom relief as compared to the control group (59 percent versus 35 percent). Also, on other outcome measures, patients taking the placebo doubled their rates of improvement to a degree roughly equivalent to the effects of the most powerful IBS medications.

"I didn't think it would work," says senior author Anthony Lembo, an HMS associate professor of medicine at BIDMC and an IBS expert. "I felt awkward asking patients to literally take a placebo. But to my surprise, it seemed to work for many of them."

The authors caution that this study is small and limited in scope and simply opens the door to the notion that placebos are effective even for fully informed patients—a hypothesis that larger trials will need to confirm.

"Nevertheless," says Kaptchuk, "these findings suggest that rather than mere positive thinking, there may be significant benefit to the very performance of medical ritual. I'm excited about studying this further. Placebos may work even when patients know they're taking placebos."

—David Cameron



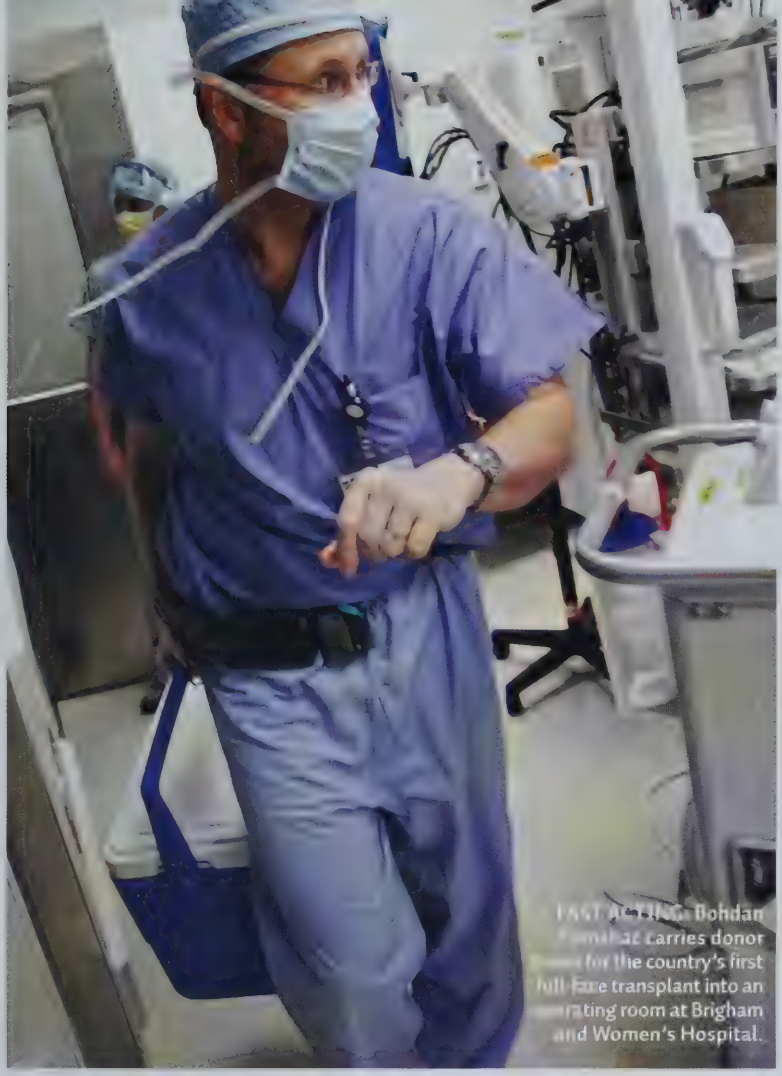
Thinking Ahead on Diabetes

DOCTORS MAY BE ABLE TO IDENTIFY people at elevated risk of developing type 2 diabetes as long as a decade before symptoms of the disorder appear by measuring the levels of small molecules in the blood.

In a March study in *Nature Medicine*, a team led by Massachusetts General Hospital researchers report that levels of five amino acids not only indicated increased diabetes risk in a general population but also could show which individuals with traditional risk factors such as obesity were most likely to develop diabetes. In addition, among individuals with traditional risk factors for type 2 diabetes, those with the highest levels of the three most predictive amino acids had a four to five times greater risk of developing diabetes than those with the lowest levels.

"These findings could provide insight into metabolic pathways that are altered early in disease development and may help us identify those at highest risk for developing diabetes," says lead author Thomas Wang, an HMS associate professor of medicine at Mass General.

—Sue McGreevey



FAST ACTING: Bohdan Pomahac carries donor tissue for the country's first full-face transplant into an operating room at Brigham and Women's Hospital.

PHOTOS: SHAWN G. HENRY (TOP LEFT); STEPHANIE MITCHELL/HARVARD NEWS OFFICE (BOTTOM LEFT); ALEXANDER HASSENSTEIN/PHOTOGRAPH BY RIGHT; ISTOCKPHOTO.COM (FAR RIGHT)

IN THE BEST TRADITION

Brigham and Women's performs full-face transplants

IN MARCH, A BRIGHAM AND WOMEN'S HOSPITAL plastic surgery team performed the country's first full-face transplant. Led by Bohdan Pomahac, an HMS assistant professor of surgery, a team of more than 30 surgeons, nurses, anesthesiologists, and residents worked for more than 15 hours to replace the facial area of patient Dallas Wiens, including his nose, lips, skin, facial-animation muscles, and nerves powering those muscles. Wiens, a 26-year-old construction worker from Fort Worth, Texas, suffered fourth-degree burns over his entire face in 2008, when the cherry picker he was working in touched a high-voltage power line.

Pomahac declared the complex procedure "a resounding success," adding that although it may take Wiens several months before he is fully able to move his facial muscles, he should make a complete recovery. The surgeon followed that feat with a second full-face transplant just weeks later.

The surgeries marked additional milestones in the hospital's legacy in transplant surgery. The Peter Bent Brigham Hospital, one of three hospitals that merged to form Brigham and Women's in 1980, made history in 1954, when a surgical team led by Joseph Murray '43B, now an HMS professor of surgery emeritus, performed the world's first successful human organ transplant.

A more recent milestone occurred in 2009, when another Brigham surgical team, also led by Pomahac, successfully performed the first partial face transplant in New England, only the second such procedure to be accomplished in the United States and the seventh such in the world.

Early Warning System

A new approach allows the diagnosis of autism spectrum disorders in infants

A NEW NONINVASIVE test may provide highly accurate evaluations of an infant's autism risk. The test, which combines the standard tool for recording electrical activity in the brain with special algorithms, has distinguished with 80-percent accuracy between nine-month-old infants known to be at high risk for autism and same-age controls.

Reported online in the journal *BMC Medicine* on February 22, the test, which captures early differences in brain organization and function, might help to identify early those infants at high risk for autism, allowing parents to begin behavioral interventions one to two years earlier than now possible.

William Bosl, a neuro-informatics researcher in the Children's Hospital Informatics Program, and Charles Nelson, research director of the Developmental Medicine Center at Children's Hospital Boston, recorded electroencephalographic activity from 79 babies aged 6 to 24 months both at rest and while watching bubbles being blown. Forty-six infants had an older sibling with an autism spectrum disorder; the others had no family history of autism.

When algorithms computed the density of neural connections in regions of the brain that had been probed, the researchers found different patterns of neural connectivity in the brains of infants at high risk for autism. The greatest difference was seen at nine months of age, when the higher-level social and communication skills begin developing.



Web-Crawling the Brain

THE BRAIN IS A BLACK BOX. A complex circuitry of neurons fires information through channels, much like the inner workings of a computer chip. But while computer processors are regimented with the deft economy of an assembly line, neural circuits are impenetrable masses. Think tumbleweed.


Clay Reid

In the March 10 issue of *Nature*, Clay Reid, an HMS professor of neurobiology, reports a technique that unravels these masses and allows researchers to "crawl" through the individual connections of a neural network.

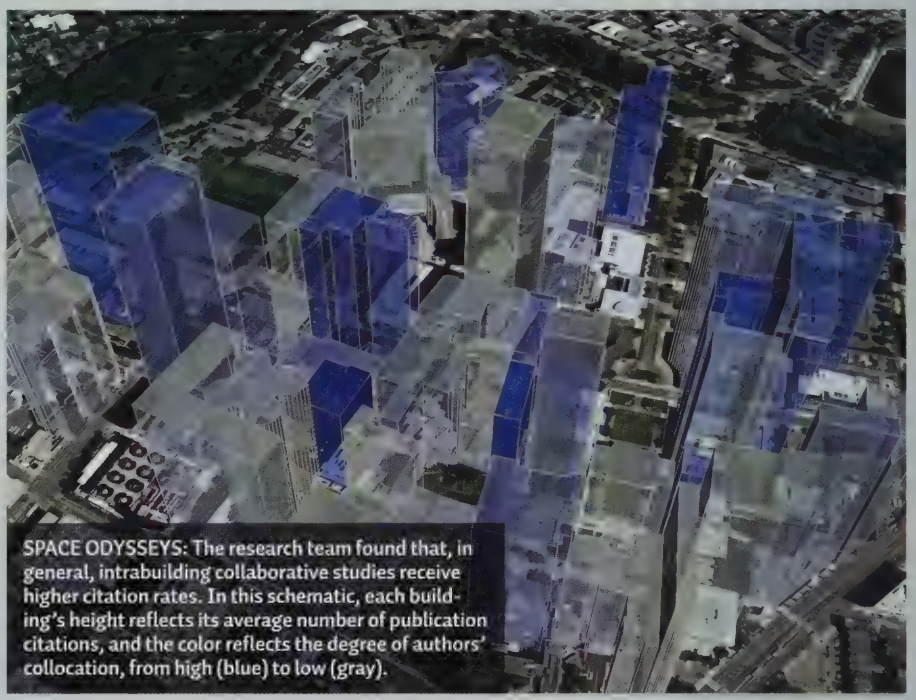
The cerebral cortex, arguably the most important part of the mammalian brain, helps us to perceive, remember, and plan. The ultimate prize for researchers would be to probe the architecture of a single cortical circuit—which contains between 10,000 and 100,000 neurons, each of which makes about 10,000 interconnections.

Reid's team embarked on a two-part study of the pinpoint-sized region of a mouse brain that is involved in processing vision. They injected the brain with dyes and recorded the flashes as specific neurons fired. The team then used electron microscopy to take nanometer-resolution images of the same neurons, which they used to trace the connections of ten individual neurons.

The team found that neurons that inhibit brain activity seem to be randomly wired, shutting down groups of neurons rather than individual ones. Such findings are important; epilepsy and other neurological conditions result from neural inhibition gone awry.

"This is just the iceberg's tip," says Reid. "Within ten years I'm convinced we'll be imaging the activity of thousands of neurons in a living brain."

—David Cameron


SPACE ODYSSEYS: The research team found that, in general, intrabuilding collaborative studies receive higher citation rates. In this schematic, each building's height reflects its average number of publication citations, and the color reflects the degree of authors' collocation, from high (blue) to low (gray).

A BEAUTIFUL DAY FOR A NEIGHBOR

ABSENCE MAKES your heart grow fonder, but close quarters may boost your career. According to research by HMS scientists, the physical proximity of researchers, especially between the first and last authors on published papers, strongly correlates with the impact of their work.

"Despite all of the profound advances in information technology, such as video conferencing, we found that physical proximity still matters for research productivity and impact," says Isaac Kohane, the Lawrence J. Henderson Professor of Pediatrics at Children's Hospital Boston and director of the Countway Library of Medicine. The research appeared in the December 15 issue of *PLoS ONE*.

Given that the Internet and social networks make it possible for people to collaborate remotely, the researchers investigated whether proximity corresponded to the scientific impact of research as measured by citations of resulting publications.

As part of the project, Kohane and colleagues analyzed life sciences articles published by Harvard investigators from 1999 to 2003. They looked at authors across four major research centers, for a total of 35,000 articles in 2,000 journals by 200,000 authors. The team then analyzed coordinates and geographic data for each location and developed a three-dimensional, high-resolution graphic to depict location-based collaborations.

The researchers found that, on average, a paper with four or fewer authors who are located in the same building was cited 45 percent more often than if the authors were in different buildings. Generally, citations decreased as the distance between first and last authors increased.

"The closer the first and last authors are located, the more impactful that paper is as measured by how much more it is cited," says Kyungjoon Lee, a research assistant in the HMS Center for Biomedical Informatics. He and Kohane suggest that these findings have implications for those who design research centers.

"The question is, ultimately, which individuals do you want to bring together?" says Kohane. "If you want people to collaborate, these findings reinforce the need to create architectures and facilities that support frequent, physical interactions. Otherwise it's really out of sight, out of mind."

—Katie DuBoff

IMAGES: KRIS SNIBBE/HARVARD NEWS OFFICE (FAR LEFT); KYUNGJOON LEE (LEFT); JON CHASE/HARVARD NEWS OFFICE (RIGHT); STOCK.XCHNG (FAR RIGHT)



BRAIN TEASERS

Amyloid plaques appear in normal elders

HMS RESEARCHERS HAVE found that cognitively normal older people with brain deposits of amyloid beta—the primary constituent of the plaques found in the brains of people with Alzheimer's disease—also had brain structure changes similar to those in Alzheimer's patients. Their study in the March 17 issue of *Annals of Neurology* may help identify candidates for therapies to prevent the development of dementia.

Definitive diagnosis of Alzheimer's disease requires finding amyloid plaques and neurofibrillary tangles in the brain at autopsy. In this study, cognitively normal older people and those diagnosed with mild Alzheimer's underwent both high-resolution magnetic resonance imaging of brain structure and PET scanning using an imaging agent known as Pittsburgh Compound B.

The cognitively normal elders who had amyloid plaques also had structural changes that were less pronounced than the neurodegenerative changes in the Alzheimer's patients.

"Our findings support the theory that Alzheimer's disease begins years before symptoms appear and that amyloid plaque is an early sign of this process," says Keith Johnson, an HMS associate professor of radiology at Massachusetts General Hospital. "When amyloid deposits are present, even in cognitively normal individuals, the degenerative changes of Alzheimer's are under way."



SIGNAL STREAM: Christopher Walsh has found that cerebrospinal fluid may hold clues to the development of brain tumors.

The Developing Brain

THE CEREBROSPINAL FLUID (CSF) that bathes the brain and spinal cord may play a larger role in the developing brain than previously thought, say researchers at Children's Hospital Boston. A paper published online March 10 in *Neuron* indicates how signals from the CSF help drive neural development and identifies a CSF protein whose levels are elevated in patients with glioblastoma, a common malignant brain tumor, suggesting a potential link between CSF signaling and brain tumor growth and regulation.

Using a mouse model, the study team noticed that these apical proteins are expressed on the parts of the stem cell that are in contact with the CSF, and that stem cells actually send tiny protruding processes called cilia, which act almost like antennae, directly into the CSF. The researchers suspected that signals to initiate or curb stem cell growth were coming from the CSF. But how? The team showed that Igf2 levels in CSF regulated the rate of stem-cell proliferation, fluctuating over time but peaking near birth, a time when the cortex is actively developing.

"The CSF is really telling the brain what to do," says senior investigator Christopher Walsh, Bullard Professor of Pediatrics and Neurology and chief of the Division of Genetics at Children's. "It's telling the stem cells to either divide a lot if you're in the embryonic brain, or if you're in the adult brain, just rest, and we'll tell you if we need you."

A better understanding of this process could lead to increased understanding of some brain tumors, including glioblastoma.

On Fertile Grounds

Leptin may restore reproductive fitness in thin women

WOMEN WITH EXTREMELY LOW body fat, including runners and dancers, as well as women with eating disorders, are prone to develop hypothalamic amenorrhea, a condition in which their menstrual periods cease, triggering such serious problems as infertility and osteoporosis.

Now, a study led by researchers at Beth Israel Deaconess Medical Center offers the first definitive proof that a lack of leptin contributes to hypothalamic amenorrhea and that treatment with a synthetic form of the hormone can restore fertility and reduce the risk of bone fractures. The findings were reported online April 4 in the *Proceedings of the National Academy of Sciences*.

"Our findings now prove that leptin is the missing link in women with significantly diminished body fat," explains senior author Christos Mantzoros, an HMS professor of medicine and director of the Human Nutrition Unit at Beth Israel Deaconess. Without leptin, menstrual periods cease, the body becomes chronically energy-deprived, and women experience bone loss and an increased risk of bone fractures.

The study followed 20 women, 18 to 35 years of age, with hypothalamic amenorrhea. Over 36 weeks, the women received either daily subcutaneous injections of a synthetic form of leptin or a placebo. Within a month of treatment, hormone levels in women receiving replacement leptin had risen significantly, with many again ovulating and menstruating.

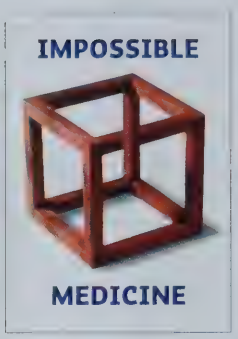
Mantzoros says the team will next examine whether synthetic leptin affects bone density and bone mineral content, factors key to preventing stress fractures and osteoporosis.

—*Bonnie Prescott*



Why do Harvard doctors remain undaunted by the demands of discovery?





The Discovery Channel

by CATHRYN DELUDE

ON ONE RIDGE stand scientists clutching discoveries rich with possibility; along another are physicians reaching for therapies to alleviate their patients' suffering. Between them runs an abyss, its floor strewn with abandoned drug candidates and failed clinical trials. ■ Into this chasm ventured two unsuspecting Harvard Medical School neurobiology professors, Clifford Woolf and Bruce Bean. After years of collaboration, the scientists wanted to use their experience in deciphering the neurophysiology of pain to develop a new generation of analgesics. Joining forces with a group of neurobiologists and clinicians, they sought venture capital. In 2006, the group launched Solace Pharmaceuticals with a plan to translate several key discoveries into new drugs—and to bridge the gaps between bench and bedside, basic and applied science, academia and the pharmaceutical industry.

Neither Woolf nor Bean had attempted anything like this before, and they found that the journey from idea to drug carried a steeper learning curve and more steps—seeking a patent, licensing the technology, raising money for further testing, among many others—than either had anticipated. Nevertheless, their plan seemed to proceed flawlessly, and they quickly identified a compound that relieved pain in rats. Then came the giant hurdle of translation to human clinical trials.

"The results were beautifully clear," says Woolf. "The drug didn't work in humans."

The researchers had experienced a common obstacle: molecular processes in animals don't necessarily translate to human biology. Their drug failed in a proof-of-principle trial and never made it to more extensive Phase II and III trials. Even if the drug had shown promise, other obstacles—including safety, regulatory, and financial ones—might well have derailed their work down the road. For every new drug that makes it to market, at least a hundred promising compounds fail at an experimental stage. Many biomedical researchers put the chances of a discovery surviving the trip to market more simply: it is a journey through the Valley of Death.

And academics are ill equipped to traverse that valley alone. "Medical schools aren't set up to do small-scale proof-of-principle human clinical trials, much less large-scale ones, and scientists aren't used to navigating regulatory issues," says Jeffrey Flier, dean of HMS. "Those capacities lie in industry."

But the road can be treacherous for the pharmaceutical industry as well. Nine of ten potential medicines entering clinical trials fail. High-profile, late-stage drug failures have cost Big Pharma billions of dollars and prompted the industry to seek new, innovative approaches to drug discovery and development. These approaches include closer collaborations with academic institutions, from which, says Flier, "most of the fundamental discoveries come."

Meanwhile, many brilliant university-based discoveries with true drug-development potential "just get left on the pages of medical journals," says Frances Jensen, an HMS professor of neurology and director of epilepsy research at Children's Hospital Boston. "At the basic science level, scientists might do great research, get their results published in a high-profile journal, and then move on to the next fundamental experiment. Their discovery just sits on a shelf. Nobody picks it up, and nobody takes the next step of translation."

Even when promising ideas get noticed, universities lack the resources and know-how to develop them. The continued shrinking of research dollars adds more pressure to an already competitive process. And industry is cutting budgets as well.

These forces have created what one HMS official calls "a perfect storm." But the School is creating shelters for those willing to brave the tempest.

At the Center of Discovery

Around the time that Solace halted clinical trials of the pain medication that Woolf and Bean had developed, the National Institutes of Health was unveiling an initiative—eventually expected to surpass $500 million a year—to address the very issues that had caused the researchers grief. Universities and medical centers around the country began to vie for a share of the funds, with the hope of using them to create clinical and translational science centers, or CTSCs, designed to ease the journey from discovery to therapy.

In 2007, Flier had barely settled in his new position as dean of HMS when he learned that the NIH would be phasing out the general clinical research center grants historically awarded to Harvard's major teaching hospitals. Instead, HMS would have to apply for funding to create a CTSC to be shared with its hospital affiliates and the rest of the University. Flier pulled together a team that, under the leadership of Lee Nadler '73, crafted a winning proposal for a five-year, $117.7-million award for such a center, now known as Harvard Catalyst.

The difference between basic research and translational medicine is intent, Flier says. In basic research, scientists seek to understand fundamental biology: how a certain part of a cell works, for example, or how a molecular signal passes from cell to cell. In translational work, researchers want to frame basic science findings to capture a disease's cause or to improve its diagnosis, treatment, management, or prevention.

"We're still a long way from even a basic grasp of the mechanisms that underlie most human diseases," Flier says. "Even when we have that understanding, as we do with cystic fibrosis, for example, it's not an easy leap to therapies. Turning discoveries into effective treatments is daunting, even before

O PIONEERS!: Clifford Woolf (left) and Bruce Bean, who entered the discovery-to-drug adventure as experienced scientists but inexperienced entrepreneurs, weathered early setbacks before crafting a promising agreement to collaboratively develop their new pain medication with Endo Pharmaceuticals.



you encounter issues in funding, conflict of interest, regulation, or a host of other arenas."

To help bridge that gap, in the past few years Flier created two new posts—dean for clinical and translational research, held by Nadler, and executive dean for research, held by William Chin '72, both of whom brought significant experience in translational research and human clinical experimentation.

"Medical schools have at their heart a desire to help patients," says Chin. "We focus on basic research—using such model systems as mice, zebrafish, and fruit flies—because we need this information for insight into what leads to human disease in the first place. But remember, one of our primary goals is to alleviate human suffering caused by disease, and stopping at basic research would leave us short of that goal. So while we don't require scientists to take a translational approach, we encourage them to think about it. We're also working to make the process easier for those who do."

Sometimes, adds Nadler, the hardest step is the first one. "My colleagues who are basic scientists often tell me, 'I'd really like to pursue translational research. But I don't know what the question should be or how to proceed to the answer.'"

So Nadler, under the auspices of Harvard Catalyst, has fostered initiatives aimed at helping to frame those questions. One such initiative was a recent crowdsourcing challenge that solicited ideas—and funded research projects—based on a simple question: What do we not know to cure type 1 diabetes? This question was posed to the entire community of basic researchers, disease- and patient-focused clinicians, and technology innovators, and the wisdom of the crowd provided new approaches to an old and still vexing disease. "The effort was highly successful," says Nadler, "in that it allowed people who had never worked in the field of type 1 diabetes to share their ideas."

Chin agrees that creative collaboration is key to the School's translational research initiatives. "We want to foster more productive multidisciplinary, interdepartmental, and cross-institutional work and team

"One of our primary goals is to alleviate human suffering caused by disease, and stopping at basic research would leave us short of that goal. So while we don't require scientists to take a translational approach, we encourage them to think about it."

formation," he says. "We believe this will lead to more innovation and creativity."

But that goal bumps up against another hurdle to translational research—the culture of science. "When basic scientists have a translatable discovery," Jensen says, "they generally have to hand that discovery over to a translation scientist and then to a clinician." She adds that the incentives in academic medicine—journal publications, grants, awards, promotions—often reward individuals rather than teams. In contrast, translational and clinical work require more collaboration. "It's hard," she says, "for translational researchers to show their added value and get credit for their work."

Part of the solution, Nadler says, is to evolve the culture and incentives. "What we need is a precise question, a team of investigators with the diverse skills to solve the problem, the required tools and technologies, and incentives to bring people from disparate disciplines together. If we say we need an answer to a specific problem and then provide pilot funding for that research," he says, "we give collaborations more focus and means."

As part of its incentive-building program, Harvard Catalyst provides one-year, $50,000 pilot grants for investigations that carry a high risk of failure yet offer big payoffs if successful. "But there's a catch," says Nadler. "You can't work with anyone you've worked with before and you must reach across the University system to find a collaborative partner." In three funding cycles thus far, the program has awarded 161 grants for innovative projects aimed at, for example, engineering resistance to epileptic seizures, identifying biomarkers for Alzheimer's disease, and pinpointing neural indicators of dyslexia in infants.

Harvard Catalyst has also introduced practical courses in clinical research and translational medicine, including a weeklong introduction to clinical investigation, offered several times a year, and more advanced classes. Several affiliated hospitals offer training as well.

"Through such initiatives," says Chin, "we're creating a new breed of investigator. Basic scientists are engaged in learning about disease, and physicians are gaining backgrounds in basic science."

Another program that provides critical assistance to foster and advance translational research at HMS is the Technology Development Accelerator Fund, launched and operated by Harvard's Office of Technology Development. Fueled by donations raised from philanthropic sources, the Accelerator Fund is a grant-based program that enables investigators to bridge the often insurmountable development gap in order to establish proof-of-principle and to transform promising early-stage inventions into viable candidates for development, commercialization, and clinical application. The Accelerator Fund has provided seed funding for 27 projects at the level of approximately $200,000 each.

"Our primary motivation is to accelerate the development of promising new inventions that might otherwise languish for lack of support and validation, and to ensure that they're expeditiously translated for the public good," says Isaac Kohlberg, the University's chief technology development officer. "We can't predict or pick 'winners' with certainty. It's all about planting the right seeds, nurturing the seedlings, encouraging them to blossom, and weeding when necessary. Every now and then we'll be rewarded with a prize-winning flower, but we need to seed and cultivate constantly."



"Through such initiatives, we're creating a new breed of investigator. Basic scientists are engaged in learning about disease, and physicians are gaining backgrounds in basic science."

PHOTO: PATRICIA GOSLING



RECEPTIVE MANNER: Epilepsy researcher Frances Jensen found that using a safe, approved diuretic that lowers the number of chloride receptors in the brains of epileptic infants helped the babies respond to an antiseizure medication.

Tending the Gap

Jensen had no such assistance when she ventured into the foreign landscape of translational medicine two decades ago, on a search for a new drug to control seizures in newborns. She had long been fascinated by synaptic plasticity—how synapses, or the connections between neurons, grow with experience. Now she wanted to apply her knowledge to heal injuries to the infant brain.

Such an approach—translating findings on rodent brains into aids for human infants—requires a delicate pairing of basic researcher and clinician. "But in my department, as in many departments, the clinicians don't know many of the basic scientists all that well," Jensen says. The gulf between the laboratory and clinic, researcher and physician, and animal model and human patient is a major obstacle in the translational journey. Yet increasingly, people on both sides of the gap are working to bridge it.

"As clinical medicine advances and as diagnostic tools, such as biomarkers and genetics, continue their rapid evolution, we'll discover new areas of science, ones that you have to go to the bench to study," Jensen says. "In some cases we're discovering that some pathways involved in one disease process are surprisingly also important in another, seemingly unrelated disease process"—or, as Jensen's work on controlling seizures in infants shows, that a drug intended for one disease may be effective against a vastly different disease.

Medications that control seizures in adults, for example, work only half the time in infants. From research in animal models, Jensen knew that antiseizure drugs work by targeting inhibitory synapses. But infant brains have fewer inhibitory and more excitatory synapses than adult brains do. "If you give babies a drug that targets inhibitory receptors," Jensen says, "you'll find they don't have enough receptors for the drug to work."

A number of laboratories had shown that lowering the number of chloride receptors inside infant brain cells causes them to respond to a drug that targets inhibitory synapses. It turned out that bumetanide, a long-used, federally approved diuretic, targets chloride receptors in the kidney. These receptors also are found in human brains, with the numbers found in infant brains surpassing those in adult brains. To win the U.S. Food and Drug Administration's approval for repurposing this drug for infant epilepsy, Jensen and her colleagues had to prove that the drug targeted neural chloride receptors in animal brains, and then show that such receptors were also in the human brain.

Jensen's team then encountered the first of several regulatory hurdles that precede clinical trials—the institutional review board, or IRB, which ensures patient safety. Because Jensen's trial would involve three Harvard hospitals—Brigham and Women's, Children's, and Massachusetts General—it needed approvals from three separate IRBs. "It took about 18 months," Jensen recalls. That process has since been streamlined through a combined IRB, thanks to Harvard Catalyst.

Jensen hopes to tap this eased process when a new mechanism she is investigating, one that blocks the progression to epilepsy, moves from animal to human studies. But since this mechanism might be a new rather than a repurposed agent, yet more steps—involving, for instance, medicinal chemistry, toxicology, and drug metabolism—may be required. For those steps, academic institutions, which rarely have the needed expertise or infrastructure, often need to contract with industry.

Captains of Industry

Randall King '97 and Daniel Finley stumbled upon those limitations while shepherding a new molecule, one that helps rid human brain cells of the misfolded proteins implicated in Alzheimer's and other neurodegenerative diseases, through the gauntlet needed to prove its investment value to potential industry collaborators.

King and Finley were exploring why ubiquitin, a small regulatory protein that normally helps neurons dispose of misfolded proteins, sometimes fails. Wayward proteins accumulate, forming the signature plaques of neurodegenerative diseases. Finley, an HMS professor of cell biology, and King, an HMS associate professor of cell biology, discovered that, in cell cultures, the enzyme Usp14 slows the degradation of an Alzheimer's disease–linked protein. So the researchers began to hunt for a Usp14 inhibitor.

They worked with Byung-Hoon Lee, an HMS research fellow in cell biology who, using the School's Institute of Chemistry and Cell Biology–Longwood screening facility, developed a high-throughput–screening assay to search for molecules that inhibited only Usp14. The strongest candidate, christened IU1, easily entered both mouse and human cells in cultures and boosted ubiquitin's beneficial activity. Although the results were good, they weren't attractive enough for investors. "Pharmaceutical companies tend to have a weak appetite for risk," says King.

To make their invention more viable for development and commercialization, the researchers needed to demonstrate that the molecule could penetrate neurons. And they needed to boost the molecule's potency. Those steps required more medicinal chemistry than they could provide. It was a perfect project for the Accelerator Fund.

Kohlberg, who oversees the program, says this early stage of technology development is where many promising university



PACKAGE DEAL: To better their chances of catching the eye of an industry collaborator, Randall King (pictured) and Daniel Finley tapped a special gap-funding program to research improvements to the uptake and potency of a compound that could help degrade proteins linked with Alzheimer's disease.

PHOTO: JOHN SOARES

technologies run aground. "The Accelerator Fund enables early innovations to achieve preliminary validation," he says, "and selects early-stage technologies that manifest significant translational promise."

King and Finley now have a compound that not only can cross the blood–brain barrier but is also ten times more potent than the previous compound. "That work made the innovation more attractive to potential industry partners," says King. As a result, OTD identified potential partners, held discussions with a number of industry groups, and recently concluded a major agreement with a biotech company, Proteostasis Therapeutics, for the development and commercialization of this technology.

"This progress would have been impossible without the Accelerator Fund," Kohlberg says. "The fund not only supported the project, enabling the key medicinal chemistry work to be done, but also devised an effective intellectual property strategy and undertook a dedicated marketing and licensing program. All of these steps culminated in our now having a strong industry partner that's committed to the commercial development of this technology and that can, we hope, take it to the clinic in the near future."

If all goes well, Finley points out, it will still be two to three years before the scientists can test their molecule in human studies.

Doctoring Peppers

Even after their disappointing first attempt, Clifford Woolf and Bruce Bean wanted to see their work result in pain medications. As they pondered new approaches, they came up with chili peppers.

Bean knew that capsaicin, the molecule that puts the sizzle in certain peppers, opens a channel called TRPV1 in pain-sensing nerve cells. A scientist seeking to alleviate pain in a research model would normally try to block this channel. But Bean and Woolf realized they could also use capsaicin as a way to guide and deliver a painkiller inside pain-sensing neurons without affecting muscles or other neurons. When considering which pain medication to pair with capsaicin for delivery, the researchers hit upon QX-314, a derivative of the common anesthetic lidocaine. Their vision: a capsaicin/QX-314 package delivered through local injection to ease the pain of childbirth and postsurgical pain.

"The right to disseminate research results is sacrosanct. In all of our agreements with industry, we make certain that the right to publish is inviolable—it is absolutely protected and guaranteed."

The time seemed ripe to pursue an industry partner for development and commercialization. This time, OTD identified and held discussions with a number of established companies with relevant expertise. Those discussions led to the negotiation and conclusion of a major licensing and collaboration agreement with Endo Pharmaceuticals, which will navigate the regulatory hurdles when it comes time to apply for safety trials in humans, possibly next year.

The imperatives of translational medicine and the importance of collaborating with industry are inextricably related, Kohlberg says. "With rare exception," he adds, "it's only through licensing and collaboration with industry partners that early-stage inventions made in academic labs can reach fruition and culminate in a new FDA-approved drug. And such a culmination in therapy represents in many ways the ultimate fulfillment of our core mission to serve the public interest."

Another important feature of agreements with industry relates to intellectual property rights and the right to publish. "When industry funds research in our laboratories, we expect to be able to publish those findings," says Flier. Industry has traditionally sought to sequester results as proprietary as often and as long as possible. More and more, though, industry realizes it's important to publish results, and researchers acknowledge the need for patent protection.

"The right to disseminate research results is sacrosanct," Kohlberg says. "In all of our agreements with industry, we make certain that the right to publish is inviolable—it is absolutely protected and guaranteed."

Previously, industry and academia each believed it could do everything alone. "In the past, partnering with industry was a bit frowned upon," Jensen recalls. "But actually, it's a necessary relationship. How else can drugs get to patients? Medical schools aren't set up to make drugs."

As for Woolf and Bean's first failed trek, not all was lost. In the reverse of a spinoff, Woolf brought one of Solace's programs back into his laboratory for further development. The path across the formerly formidable Valley of Death might just turn out to be a two-way street. ■

Cathryn Delude is a freelance writer based in Andover, Massachusetts.

Conflicts of interest

It wasn't precisely his bout with mononucleosis that led David Knipe into a career in virology. By the time Knipe, now the Higgins Professor of Microbiology and Molecular Genetics at HMS, lost a semester of college to the illness, he had been primed to become a virologist by a string of inspiring courses and a stint in a leading-edge laboratory. But the combination of illness and inspiration sealed that deal, involving Knipe in academia-based innovation, and now, with the aid of Harvard's Office of Technology Development, a licensing agreement with a manufacturer that may produce a vaccine for herpes simplex 2, the cause of genital herpes.

In his HMS laboratory, Knipe developed a replication-deficient form of the virus. In mice, the mutant virus triggered an immune response without reproducing. Knipe's hope is to develop a vaccine for humans based on the mutant. That task—and the clinical trials to test his innovation's safety and efficacy—will fall to Sanofi Pasteur. "This vaccine needs to be tested in people," says Knipe. "Without this agreement, that wouldn't happen."

At HMS, such academia–industry partnerships are carefully tended to guard against conflicts of interest, whether real or perceived. The School's policy aims to ensure that academic research remains robust and unfettered, and that industry involvement remains collaborative and fruitful. Overall, the goal is to translate ideas into powerful new medicines, devices, and technologies, a goal underscored by Jeffrey Flier, dean of Harvard Medical School, when he announced a revamped conflicts-of-interest policy last summer.

"Neither academia nor industry alone is equipped to develop the therapies so desperately needed to eradicate diseases worldwide," says Flier. "For this reason, we are committed to encouraging collaborations between our faculty and industry while ensuring the transparency of those relationships through a policy that further codifies and enforces our high standards."

The revised policy upholds the ability of HMS faculty to license technology to pharmaceutical and biotechnology companies, hold equity in such companies, serve on their scientific boards, and establish new ventures. At the same time, the policy prohibits academia–industry links that might adversely influence the integrity of such ties. Faculty can no longer accept, for example, personal gifts or any travel and meals from industry, other than those received during allowed activities. As of July 2011, faculty members are barred from participating in industry speakers' bureaus or accepting any speaking engagement that would dictate the faculty member's presentation content.

In the realm of medical education, the policy reinforces restrictions barring sales and marketing representatives of medical drug, device, or supply companies from accessing medical students. Continuing medical education courses may no longer be sponsored by a single company, and industry advertising and exhibits at continuing medical education events are restricted.

The conflicts-of-interest policy addresses the challenges of academia–industry collaborations, says Flier, while maintaining the School's commitment to advancing research in human diseases.

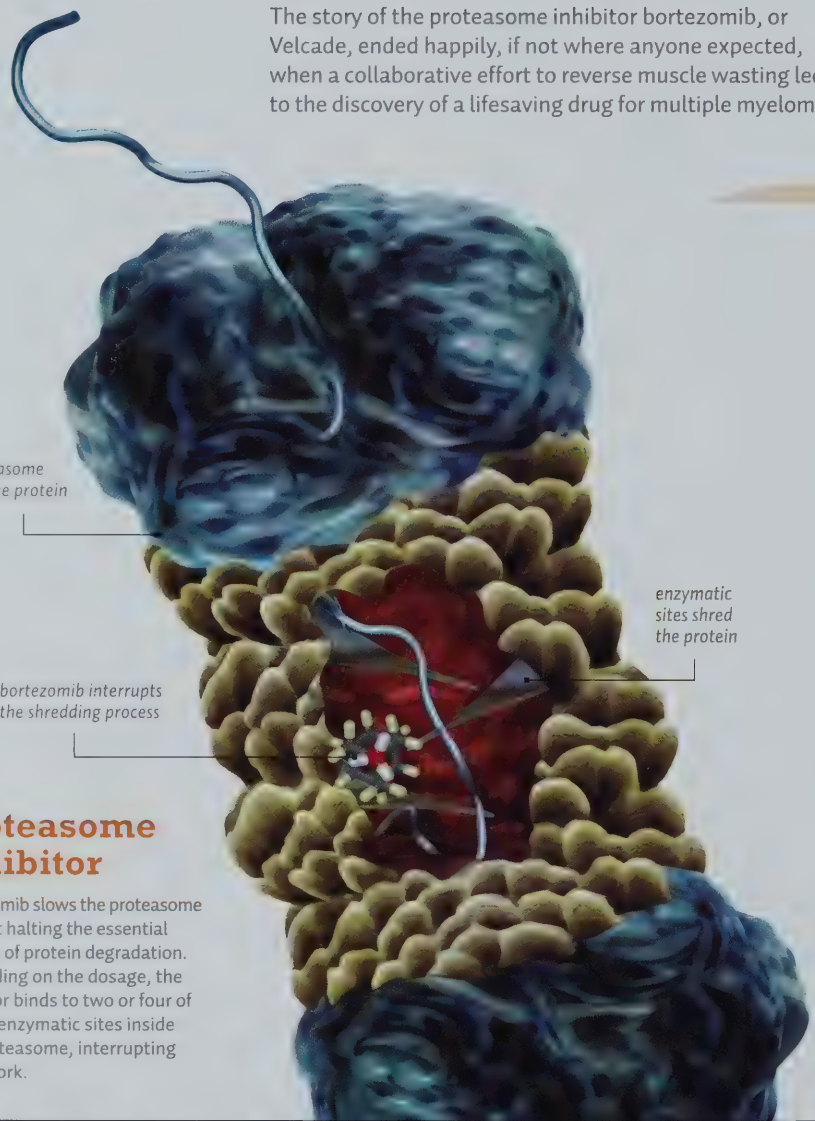
To review the policy, visit hms.harvard.edu/public/coi.

—*Ann Marie Menting*

ANATOMY OF A DISCOVERY

The Road to Velcade

The story of the proteasome inhibitor bortezomib, or Velcade, ended happily, if not where anyone expected, when a collaborative effort to reverse muscle wasting led to the discovery of a lifesaving drug for multiple myeloma.



Proteasome Inhibitor

Bortezomib slows the proteasome without halting the essential process of protein degradation. Depending on the dosage, the inhibitor binds to two or four of the six enzymatic sites inside the proteasome, interrupting their work.



BENCH

1966–68
Curiosity Strikes

Alfred Goldberg interrupts his medical school studies to investigate how and why muscles shrink when not used. His discovery that muscles atrophy because of excessive protein breakdown leads him to research how cells degrade proteins. Few scientists at the time showed interest in the process.

1977
An Early Discovery

Goldberg and colleagues discover a novel pathway that disposes of unneeded and misfolded proteins. They and other research teams later accumulate evidence for a cellular structure Goldberg eventually names the proteasome. Until then, scientists believed that proteins were degraded only in a structure called the lysosome.

1990
Putting It to the Test

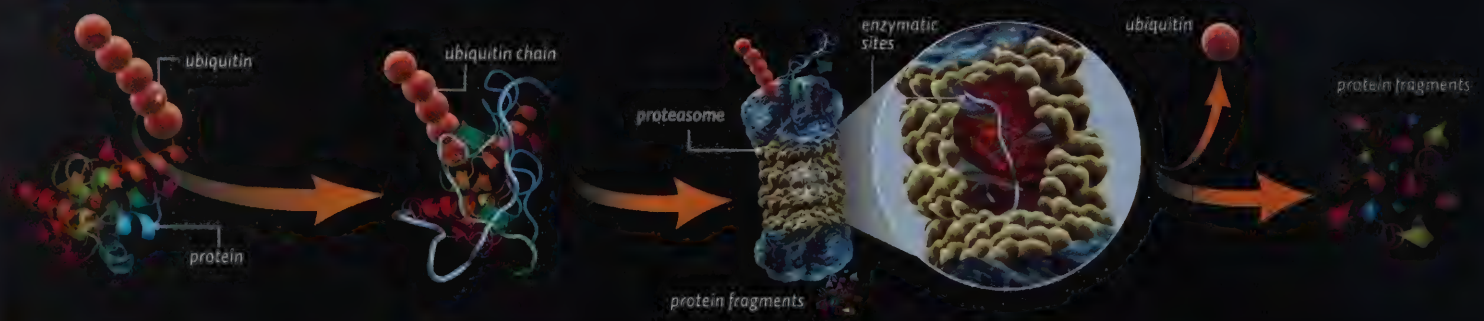
Insights from parallel experiments in biochemistry and physiology lead Goldberg to speculate that inhibiting the proteasome might slow the muscle wasting that accompanies many diseases.

1993
A Do-It-Yourself Project

Goldberg gathers a group of Harvard faculty members to establish a company, MyoGenics, aimed at bringing scientists from disparate fields together to understand how to inhibit the proteasome to slow muscle wasting and perhaps treat a range of diseases.

GRAPHIC: CHRISTINA ULLMAN TEXT: ELIZABETH DOUGHERTY

The Proteasome HOW IT WORKS



1. By "tagging" a protein with tiny ubiquitin molecules, a cell marks that protein for immediate disposal.
2. The barrel-shaped proteasome latches onto a tagged protein, releases the ubiquitin, unravels the protein, and pulls it inside.
3. The wall of the proteasome contains enzymatic sites that shred the protein into small framents.
4. The proteasome releases the protein fragments, and other enzymes degrade them further to their consitutent amino acids.

1994–96
An Unexpected Link

Researchers from Goldberg's laboratory and MyoGenics demonstrate that inhibitions of the proteasome can block protein breakdown in cells. Scientists across the country use MyoGenics-developed molecules to inhibit the proteasome. To their surprise, a possible cancer connection emerges.

1999
A Major Setback

Despite mounting scientific successes, the company, since renamed ProScript, runs out of funding. It is acquired by a company called Leukosite, which is in turn acquired by Millennium Pharmaceuticals.

2001
Powers of Persuasion

Adams and Anderson convince Millennium leadership to move forward with a Phase II trial of bortezomib in people with multiple myeloma.

2002
Hard Work Rewarded

Anderson and Paul Richardson lead the Phase II trial, which shows remarkable results.

2003–2007
Double Check

Even though bortezomib, now commercially known as Velcade, has already been approved, the U.S. Food and Drug Administration asks investigators to proceed with confirmatory Phase III clinical trials. Richardson leads the effort.

2010
Combination Lock

Richardson spearheads multicenter clinical trials investigating novel drug combinations using Velcade; a triple-drug cocktail is approved as a first-line therapy.

2011
Continued Promise

Since its approval, Velcade has been used to treat more than 230,000 people with multiple myeloma. In the laboratory, proteasome inhibitors have influenced nearly all areas of biomedicine, as evidenced by more than 3,000 citations in scientific journals. Four other proteasome inhibitors are now in clinical trials, and researchers at Harvard and around the world are studying additional applications against cancers, autoimmune disorders, and other diseases.



1994
Tricks of the Trade

Julian Adams joins the company to help turn the initial proteasome inhibitor into a drug, eventually known as bortezomib.

1997
Opportunity Knocks

A National Cancer Institute screen of bortezomib finds it has intriguing effects against solid tumors.

2000
An Unprecedented Result

In Phase I trials of the inhibitor, a patient with multiple myeloma shows a rapid and complete remission.

2000
Early Promise

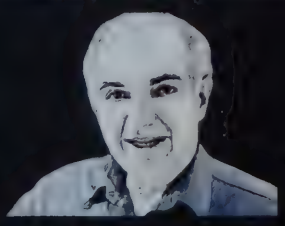
Researchers at Dana–Farber Cancer Institute, led by Kenneth Anderson, and scientists elsewhere show that bortezomib is particularly active against myeloma cells in the laboratory.

2003
Drug Approval

The U.S. Food and Drug Administration approves bortezomib for treatment of multiple myeloma just four months after submission of the application—remarkably, even before Phase III trials have been conducted.

TO LEARN MORE, WATCH *FOUND IN TRANSLATION,* A VIDEO COMPANION TO THIS FEATURE, ON HARVARDMEDICINE.HMS.HARVARD.EDU

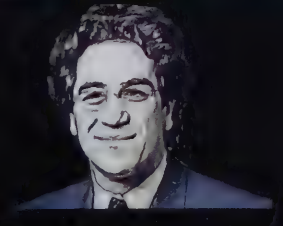
Champions of Invention HOW THEY INNOVATED



Alfred Goldberg

HMS Professor of Cell Biology

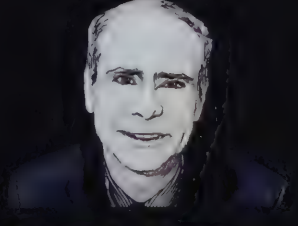
By joining the biochemistry of a proteasome with its physiology, the "grandfather" of Velcade became the first to imagine the therapeutic value of a proteasome inhibitor. He also founded a company to pursue his vision for blocking proteasome action.



Julian Adams

Chief Scientific Officer and Senior Vice President of Research and Development, Infinity Pharmaceuticals, Inc.

This pharmaceutical veteran created a potent inhibitor, developed it into a safe drug, and amassed scientific data that quelled toxicity concerns.



Kenneth Anderson

Kraft Family Professor of Medicine, HMS and Dana–Farber Cancer Institute

After a Phase I trial stumbled upon multiple myeloma as a disease target, Anderson joined Adams in convincing Millennium Pharmaceuticals to invest in a Phase II trial. With Paul Richardson, Anderson went on to lead the trial.



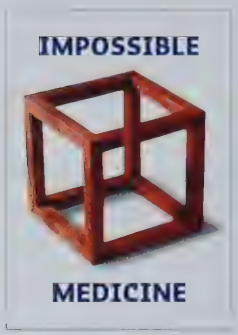
Paul Richardson

HMS Associate Professor of Medicine, Dana–Farber Cancer Institute

Richardson led Phase II and III trials of the drug. Since then, he has spearheaded multicenter clinical trials of novel drug combinations using Velcade. A triple-drug combination has shown promise.



THE INGENIOUS GENTLEMAN: Before William Chin '72 assumed the role of executive dean for research at Harvard Medical School in 2010, he worked at Eli Lilly and Company for more than a decade, most recently as senior vice president for discovery research and clinical investigation. Prior to that, Chin was a molecular endocrinologist at Brigham and Women's Hospital, where he investigated the structure, function, and regulation of genes that code for hormones.



This Glorious Quest

William Chin, Harvard Medical School's executive dean for research, offers a vision for partnerships that move discoveries from bench to bedside

interview by DAVID CAMERON



Q: You've likened the researcher's path of discovery to Don Quixote's quest. Can you elaborate?
A: Don Quixote relied on imagination, determination, and luck, and researchers need all three to prevail—along with an unwavering sense of optimism in the face of ongoing defeat. That's the nature of scientific inquiry. Nowhere is that sense of optimism more needed than in drug discovery, which seeks to identify and develop potential medicines that provide a favorable and delicate balance of effectiveness against disease while ensuring safety.

Q: How has drug discovery evolved?
A: Thirty or more years ago, the discovery of new medicines was based on the observation that a chemical or an herbal extract had a biological effect. Scientists would then tweak the chemical or molecule to make it safe and effective in humans. That's the classic pharmacological approach.

Another, newer approach is based on knowledge we've gained during the genomic revolution. We can now begin with a gene that we believe relates to a particular disease, then either increase or suppress the activity of that gene in the hope of discovering its precise role in that particular condition. We take multiple shots in hopes of scoring a goal.

Q: And then you screen a million compounds?
A: Yes, but that adds a new level of complexity. Even if we find a molecule that hits a target, we still don't know exactly how that target links to a disease. A major reason the pharmaceutical industry has failed to be as productive as we'd like is that we have yet to pinpoint the root causes of most diseases. Nor do we understand the natural variation in disease that occurs across

patients. Not everyone with type 2 diabetes, for example, has exactly the same disease. Not all breast cancers or lung cancers stem from the same cause, even if they behave similarly in a biological sense. If you don't know the cause of a disease and you try to cure that disease with a guess, chances are you'll fail.

So if you think about the notion of "impossible medicine"—treatment goals that might seem unreachable—yes, medicine becomes far less possible when you don't know what causes disease. To make good medicine possible, we need to focus on the basic biology of disease.

Q: Can you give some examples of biomedical discoveries that proved attainable against great odds?
A: Vaccines have been tremendous successes. When I was a kid, everyone was deathly afraid of polio. Polio has since been largely cured, as have many childhood diseases.

Antibiotics have proved to be triumphs as well—against pneumonia, urinary tract infections, even tuberculosis. And multiple drug therapies can now control HIV disease—provided people with the virus can access those medicines.

Going back a bit further, the discovery of insulin was remarkable, and that finding isn't yet a century old. Before insulin, doctors essentially lowered patients' blood sugar through starvation!

Q: Did the discovery of insulin occur in academia or in industry?
A: The answer to that is fascinating. In the early 1920s, two university researchers, Frederick Banting and Charles Best, discovered how to make an extract from the pancreases of cows and pigs that could treat diabetes in humans. This finding, incidentally, earned Banting and a collaborator a Nobel Prize. But when these researchers tried to make batches of insulin, they lacked a method for making a pharmacologically uniform drug. Standardization is critical in drug production.

So the head of research at Eli Lilly—where I worked for eleven years—went to Toronto and said, "Look, we can help you make uniform batches." Lilly became the first company to produce a standardized insulin.

More recently, statins—medicines aimed at lowering blood cholesterol—have helped many people, as have antihypertensives. And in the realm of cancer, we've had Gleevec, Tarceva, Iressa, and Herceptin. These are just a handful of the contributions pharmaceutical companies have made during the past few decades, most in collaboration with academia.

Q: How many of these drugs were developed under the more classic, randomized approach?
A: Most of them, although the development of statins came from a combination of new and old approaches. In truth, the original statin was discovered almost by accident: the researcher was actually looking for an antifungal, and then others realized the statin's possible role in lowering bad cholesterol. In another example of serendipity, the breast cancer drug tamoxifen also was found to be a treatment for osteoporosis. And Viagra, remember, was supposed to be a heart medication.

Q: What are the biggest challenges in drug discovery?
A: We still don't have many medications to offer for schizophrenia, obesity, and a number of cancers, to name a few unmet medical needs. We know how to control type 1 diabetes mellitus, but we can't stop its development. The list goes on. Millions of people worldwide suffer from major illnesses for which we have no effective therapies.

Q: Can you give examples of how our understanding of a disease's cause led to a drug?
A: One great example is Gaucher's disease, a condition that affects the liver, bone marrow, and other tissues. People with that disease lack the enzyme glucocerebrosidase, which regulates the production of blood fats, or lipids, that are important for these organs. But Genzyme has been able to reproduce that enzyme and thus save lives.

Another example is sickle cell anemia, in which a gene defect causes hemoglobin to malfunction. Ordinarily, such a mutation would have been selected out through the process of evolution, except that it proved to confer a genetic advantage to people



The problem is that the drug pipeline functions like a lottery—one in which you invest a half-billion dollars per ticket. And you have to keep on investing in that ticket until it either wins or loses.

PHOTOS, THIS STORY: MARK OSTOW

living in parts of West Africa; it reduced their chances of getting malaria. Our understanding of the cause of sickle cell anemia has led to medications that relieve its symptoms, but we still haven't cured it.

Q: That's true of Huntington's disease, amyotrophic lateral sclerosis, and cystic fibrosis—we know the causes but don't have cures.
A: Yes. I should qualify what I said earlier: Knowing the cause of a disease is just the first step. In the case of cystic fibrosis, we know all the mutations involved, yet we still don't have a cure. Imagine just how much harder it is, then, if you don't even know the cause.

Q: We often hear that the pharma pipeline is drying up.
A: The problem is that the drug pipeline functions like a lottery—one in which you invest a half-billion dollars per ticket. And you have to keep on investing in that ticket until it either wins or loses. Industry needs to recoup those investments.

You can hope that every medicine will be like Lipitor, an effective cholesterol-lowering drug that can be used safely and indefinitely. But if you keep aiming for that jackpot, what will you miss? Rare diseases, ones that affect only a few thousand people. It's amazing, too, how few companies invest in preventive medicine, like vaccines. That's one of my pet peeves.

Another problem lies in the culture of Big Pharma. Pharmaceutical companies used to think they could do everything themselves. They're slowly realizing that they need collaborative partners in academia, in government, and in nongovernmental agencies.

Q: What role can an institution like HMS play?
A: First of all, our faculty members—some of the best scientists in the world—are studying biological processes in all kinds of cells, tissues, and model organisms to understand the fundamentals of how the body works. If we at HMS could improve the way we collaborate with our colleagues in our affiliated hospitals, we could make a big dent in this question of what causes disease, because patients hold the key to answering that question. A vital role for the School, then, is to solve the problems medicine faces by combining this intellectual capital, this passion for learning, and this power to implement experiments.

We can have the perfect medicine—one that's safe and effective—but if our patients can't take that medicine because they can't afford it or don't have access to medications, then we haven't succeeded.

HMS can also provide leadership both in creating new ways of learning about the causes of diseases—by discovering new biomarkers and relevant animal models, for example—and in developing new and growing disciplines, such as chemical biology and systems pharmacology.

Q. What is systems pharmacology?
A. Think of a spider web. If you touch even a fragment of the web, the spider knows, because it immediately senses the vibrations along the web's fine filaments. When a bug lands on a web, the spider doesn't go on a long trek to find its prey. It goes directly to the spot. Why? Because it understands its network.

Systems pharmacology strives to understand how medicines work—not just how they affect one biological pathway or one molecular or genetic target, but how they affect multiple tissues, organs, and cellular pathways in an entire physiological system. HMS has just entered this arena. We have experts in systems biology, chemical biology, human genetics, biochemistry, classical pharmacology, animal models, and informatics, but we've never brought all that expertise together.

Systems pharmacology is, in fact, one of our new initiatives. When Jeff Flier became dean of HMS, he made it a central part of his mission to have the School participate more fully in the development of new therapies. So we'll soon launch an HMS program in translational science and therapeutics, which will aim to harness all the strengths of HMS both to gain a deeper understanding of what causes disease and to create molecules that can combat those causes.

Q: How do we bring people from the basic and clinical sciences together?
A: First, through education. We need to provide training to scientists who are interested in embarking on translational research. We plan to sponsor fellowships, courses, and seminars. We'll also create a culture that better appreciates the value of translational work.

The School has and always will place tremendous value on basic science. In many ways, that's central to its identity. But a critical goal is to encourage bench scientists to shift their awareness, to consider how they might apply their research to the solution of clinical problems.

What's more, we'd like to create a Harvard therapeutics commons, a meeting place—both virtual and real-life—that we could use to unite people with diverse experience and scientific backgrounds who like exploring issues surrounding translational research, not just at HMS and its affiliates, but at other institutions as well. A scientific ecosystem that is populated by experts from academia, industry, government, nongovernmental agencies, and foundations could help patients, who must be the focus of these collaborations.

Now, any collaboration between academia and industry brings up the specter of conflicts of interest. Clearly, researchers must strive always to do the right thing. But that doesn't prohibit them from working with industry or government. We live in a context of conflict—whether of interest, time, or resources. We must be honest, open, and transparent in all situations, at all times.

Q: Could you elaborate on the role of the patient in translational medicine?
A: Several months back, Paul Farmer ['90], chair of our Department of Global Health and Social Medicine, reminded me that we can have the perfect medicine—one that's safe and effective—but if our patients can't take that medicine because they can't afford it or don't have a physician or don't have access to medications, then we haven't succeeded. Translational medicine means more than just developing therapies. It means getting those therapies to patients.

All HMS departments—whether basic science, clinical science, health care policy, or global health—are critical to achieving the objectives of translational medicine. That's why HMS is such a great place. ■

David Cameron is director of external relations at Harvard Medical School.


What discoveries wer

nimaginable even a decade ago? *by* ANN MARIE MENTING



The Twilight Zone

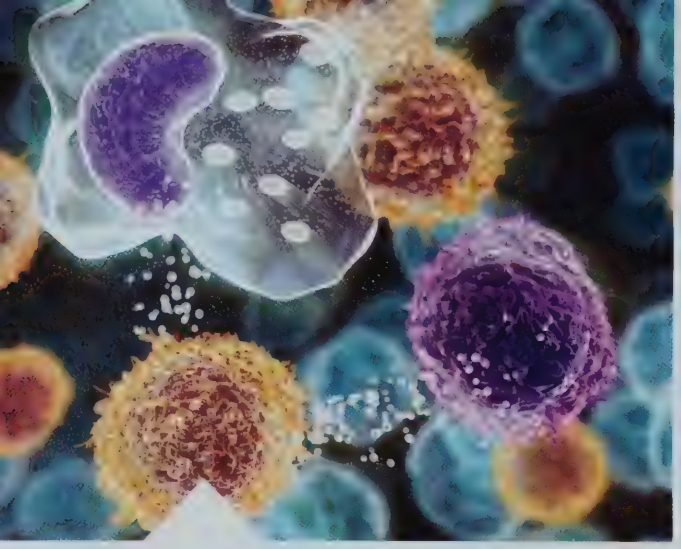
Templates from Nature

Realm of Imagination: Could DNA, that mighty molecule celebrated as the ultimate information source for biological beings, also be a font of data on nature's form and function? It is to synthetic biologists. These investigators bring a Cubist's eye to the natural world and, from each new vantage, discover unexpected therapeutic possibilities.

From Shadow to Substance: From this helical molecule, scientists such as William Shih, an HMS associate professor of biological chemistry and molecular pharmacology at the Wyss Institute for Biologically Inspired Engineering at Harvard University, tease out insights into design, stability, and self-assembly and use them to devise medical aids and treatments that are biologically effective, efficient, and sustainable. Shih and colleagues have, for example, designed scaffolds that help improve the control of enzyme-chaperoned reactions, constructed tubes and geodesic spheres that one day may ferry cancer drugs to tumor cells, and built nanoscale-sized components that, when injected into the body, could self-assemble as medical devices.

The Harvard Dimension: Advances in synthetic biology at the Wyss Institute happen, says Donald Ingber, director of the institute and the Judah Folkman Professor of Vascular Biology at HMS, because scientists think expansively, design creatively, and, with faculty and industry-seasoned technical experts, build cleverly to develop therapeutics in service to medicine. Work by Shih; Ingber; Peng Yin, an HMS assistant professor of systems biology; and other colleagues at the Wyss Institute has led to three-dimensional DNA that can be programmed to take almost any shape imaginable.

What's Next? "We will move beyond DNA to the many new classes of RNA," says Ingber, "and into gene and therapeutic delivery systems that will, for instance, be capable of changing the properties of cells and tissues in ways important to regenerating organs. Whatever we can imagine, we can build."



Inflammation's Role in Disease

Realm of Imagination: How is it possible that the body's system for initiating healing can also trigger harm? Could the inflammatory response, so recognizable when rallying to subdue the itch of an insect bite or to heal the cellular damage in a stubbed toe, also be a quiet instigator of diabetes, neurodegenerative disease, perhaps even cancer?

From Shadow to Substance: Immunology has always been a diverse area of study, yet the full scope of inflammation's role in the body has taken time to reveal itself. "Immunologists increasingly appreciate that inflammation touches many physiological systems," says Diane Mathis, an HMS professor of pathology. First was the discovery of its contribution to cardiovascular and metabolic disorders such as atherosclerosis and type 2 diabetes, followed by its links to multiple sclerosis, cardiovascular disease, and neurodegenerative diseases. Recently, interest has sharpened over whether inflammation, together with cigarette smoking and obesity, triggers some cancers.

The Harvard Dimension: Research at HMS has expanded greatly our understanding of inflammation's involvement in disease, says Mathis. Bruce Spiegelman, the Stanley J. Korsmeyer Professor of Cell Biology and Medicine at HMS, was among the first to recognize that chronic, low-grade inflammation is a link between obesity and type 2 diabetes, showing that fat cells produce mediators typically found under inflammatory conditions. Research led by Steven Shoelson, an HMS professor of medicine, has suggested that an aspirin derivative may quell this inflammation in humans with diabetes.

What's Next? "Two words will be key in the future of immunology-based therapies: natural and selective," says Mathis. "We'll discover more of the cells and molecules that participate in the body's inflammatory response and learn how to use and enhance them to inhibit disease-related inflammation. We'll also discover how to selectively deliver those inhibitors so that we can stem inflammation where it is harmful without compromising its beneficial roles in wound healing and infection fighting."

Preimplantation Genetics

Realm of Imagination: Even if a baby's health could be scripted, should it be? If screening newborns for a troubling metabolic condition helps prevent mental retardation, shouldn't screening a fertilized egg's genome for incurable conditions be a gift to would-be parents worried about the risks of lifelong disease or disorder?

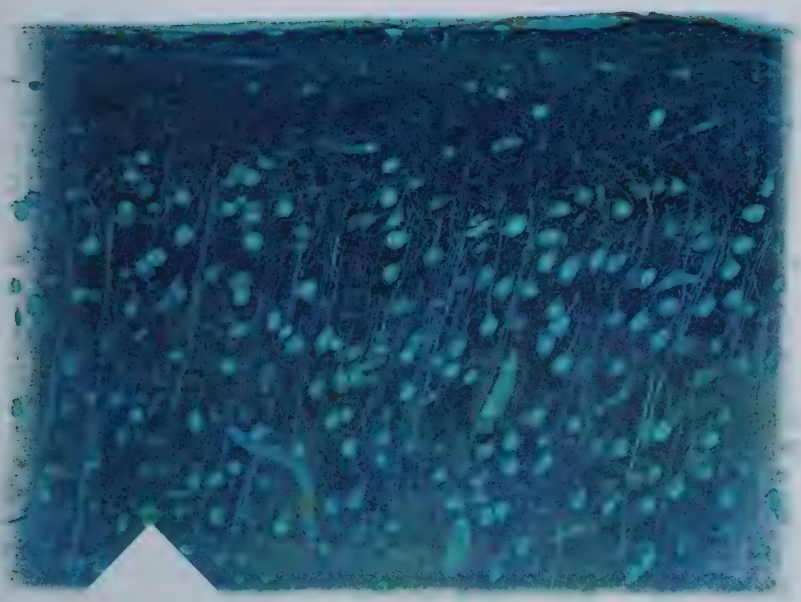
From Shadow to Substance: Until relatively recently, the idea that you could learn the information contained in your genome bordered on the unthinkable. Even more extraordinary, says Cynthia Morton, the William Lambert Richardson Professor of Obstetrics, Gynecology and Reproductive Biology and an HMS professor of pathology at Brigham and Women's Hospital, was the idea that such information could be commercially obtained. But with direct-to-consumer groups providing on-demand genetic testing and the cost of genome sequencing dropping—from $3 billion in 2003, to projections of $1,000 by 2014—Morton adds, the field is off and running.

The Harvard Dimension: The Personal Genetics Education Project, an effort directed by Ting Wu, an HMS professor of genetics, addresses the social and ethical issues of personal genetics through interactive workshops for high school students. Those same social and ethical issues are core to the Genomic Medicine Leadership Program, which Morton helped spur at Brigham and Women's. This program aims to prepare primary care doctors for their patients' questions; a key component of that preparation comes when the participants receive their own genetic profiles.

What's Next? "We will develop more sophisticated computer algorithms to help us interpret which genetic variants cause disease," says Morton. "This is not a trivial undertaking; we need this information to answer the questions people will have. I could imagine, for instance, a Facebook group for people who share a mitochondrial haplotype, one relating them to some woman who lived 30,000 years ago in the Caucasus, perhaps. And I expect that soon every newborn screen will include a genome sequence."



IMAGES: COURTESY OF F. HOFFMANN-LA ROCHE LTD. (LEFT); ALEXANDR MITIUC/ISTOCKPHOTO.COM



Neurons Made Visible

Realm of Imagination: What if we could make visible the workings of the brain? What understanding of neurological function might develop if we could watch the brain's millions of neurons in action and trace the thousands of connections each make?

From Shadow to Substance: Our knowledge of what neurons do began not with sight, but with sound. In the 1960s, Nobel Prize recipients David Hubel, the John Enders University Professor of Neurobiology Emeritus at HMS, and his former HMS colleague Torsten Wiesel placed electrodes within a living mammalian brain and listened to neurons at work. Groundbreaking as this was, it was like "listening in the dark," says Clay Reid, an HMS professor of neurobiology. "You had no idea what the neuron you were eavesdropping on looked like." The chance to glimpse busy neurons improved with the advent of the two-photon microscope, a laser-based scanning microscope, and the creation of fluorescent molecules that brighten when neurons are active.

The Harvard Dimension: In 2002, Reid first used the two-photon microscope at HMS to view neural activity in the living brain. Since then, the list of neurobiology colleagues who regularly use the tool has grown: professors Wade Regehr, David Corey, and Bernardo Sabatini; associate professor Rachel Wilson; and assistant professor Robert Datta all use the two-photon microscope in their research, for example. In 2009, Sabatini customized the tool, bringing into focus the details of synapses, structures through which neurons talk to each other, as well as of dendritic spines, lollipop-like structures that support the synapses.

What's Next? "High-end light microscopy will develop as a field," says Reid. "We will be able to gather astonishingly large data sets from the functioning brain. We'll capture images of entire neural circuits to see many thousands of neurons doing their job in a living brain, and, with electron microscopy, we'll then study the connections between these cells. Brain circuits in all their complexity will finally be visible."

PHOTOS: COURTESY OF CLAY REID, DAVI BOCK, AND WEI-CHUNG LEE (ABOVE); COURTESY OF REKESH KARMACHARYA/BROAD INSTITUTE AND MCLEAN HOSPITAL

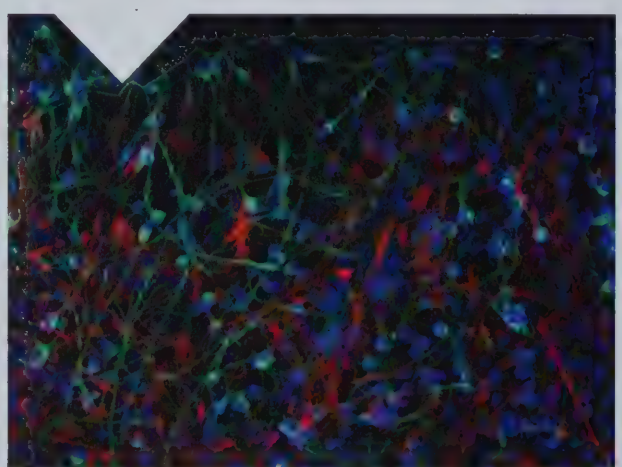
Reprogrammable Adult Stem Cells

Realm of Imagination: What if the body's cells could be instructed to treat disease or repair damage? The notion of healing at the cellular level has long tantalized researchers. Embryonic stem cells brought promise—then pitfalls. What was needed was a readily accessible supply of adult cells that, like their embryonic progenitors, were willing to assume new roles.

From Shadow to Substance: Building upon the knowledge that nearly all cells harbor the same genetic code, researchers have searched for ways to reprogram differentiated adult cells. In 2006, they discovered key reprogramming tools: a mere four molecular factors that could take differentiated cells, strip them of their adult identities, and then coax them to develop into new cell types—converting skin cells into liver cells, for example. These induced pluripotent stem, or iPS, cells rocked the world of medical research. "It was a huge, unanticipated breakthrough," says George Daley, an HMS professor of biological chemistry and molecular pharmacology. "The idea that we could turn specialized cells back into embryonic stem cells had been the stuff of science fiction."

The Harvard Dimension: The news that such a small set of factors could alter the fates of cells was met with some skepticism, says Daley. But Konrad Hochedlinger, an HMS assistant professor of medicine, refined the technique, and Daley's lab showed it worked in human cells. Daley's group has also built a large repository of disease-specific cells that can be used to test therapies. Other Harvard researchers are expanding the list of cells that can be reprogrammed and are developing new methods for making cells reprogrammable.

What's Next? "There are so many things going on in stem cell research," says Daley, "that it wouldn't surprise me if in another ten years we achieve something momentous—regenerating an organ, like a heart or liver, or tissue, like bone marrow, which is what we're trying to develop in my lab. And along the way, we might be able to correct any genetic defects in those repurposed cells."





The Underpinnings of Neurodegeneration

Realm of Imagination: Why do the plaques and tangles of Alzheimer's disease appear in the brain's connection pathways and not also in its sensory, motor, or primary speech centers? And why are the dopamine-killing lesions of Parkinson's disease only found deep within the brain's movement-control center?

From Shadow to Substance: The puzzlement surrounding Alzheimer's and Parkinson's has been clearing as researchers identify proteins key to the development of these diseases. Their discoveries have also taught us more about the brain. "One lesson," says Joseph Martin, the Edward R. and Anne G. Lefler Professor of Neurobiology at HMS, "is that the brain is never 'off.'" Even when we sleep, the brain is at work. Especially busy are its connection pathways. Recent studies have shown that these pathways are focal points for aggregation of the protein amyloid beta. As a person develops Alzheimer's, amyloid beta gums up in synapses, causing neuron-to-neuron connections—and the ability to form memories—to break down. Other work has advanced our knowledge of the genetic basis of neurodegeneration by finding that a gene defect in some people with Parkinson's leads to the production of the protein alpha synuclein, the agent that kills dopamine-producing brain cells.

The Harvard Dimension: "The best collaborative efforts at HMS," says Martin, "are those between a basic science researcher and a clinician in a hospital laboratory." A recent collaboration between neurobiology professor Bernardo Sabatini and Dennis Selkoe, the Vincent and Stella Coates Professor of Neurologic Diseases at Brigham and Women's Hospital, identified how amyloid beta interferes with synaptic modulation of memory circuits. The Harvard NeuroDiscovery Center, another collaborative effort, aims to understand and find treatments for Alzheimer's, Parkinson's, and other neurodegenerative diseases by pooling Harvard-based expertise.

What's Next? "Neurodegenerative disease research is at a great stage in its development, similar to where research on heart diseases was 30 years ago," says Martin. "Genetic pathways will help us identify specific targeted molecular drugs for these diseases."

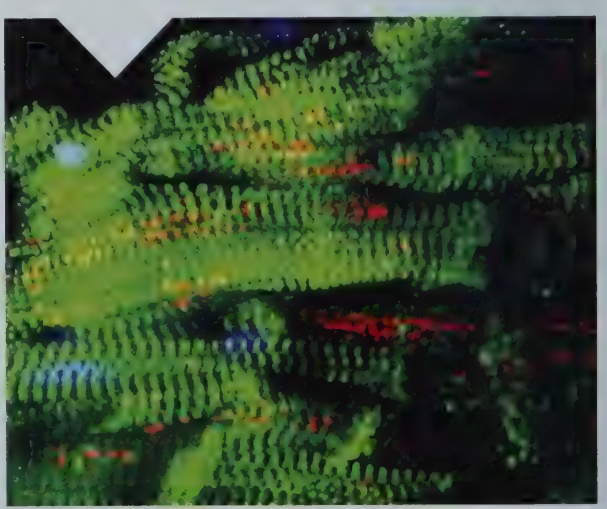
Regenerative Cells

Realm of Imagination: When a person's heart, kidney, or lung falters, physicians largely rely on the organ to heal itself, or drugs to boost its function, or transplantation to give new hope. But each carries risks. Wouldn't it be best if organs could reliably repair themselves? Wouldn't it be grand if medicine could harness the body's potential for regeneration?

From Shadow to Substance: Working with induced pluripotent stem cells, Kenneth Chien, the Charles Addison and Elizabeth Ann Sanders Professor of Basic Science at HMS, has sought to make tissue that mends the muscle of failing hearts. About five years ago, he startled the field of regenerative medicine by discovering a progenitor cell that could generate functioning strips of mature heart muscle tissue. Then he identified a "master" cardiovascular stem cell, one that gives rise to cardiac, smooth muscle, and endothelial heart cells; may help form heart muscle and coronary arteries; and may play a role in the heart's pacemaker system. The value of such a cell is enormous; it holds the potential for uncovering the origins of the human heart as well as for new therapies that repair, replace, or renew damaged tissue.

The Harvard Dimension: One leader in the field, Douglas Melton, co-chair of the Department of Stem Cell and Regenerative Biology at HMS and co-director of the Harvard Stem Cell Institute, provided early inspiration when he generated specific cell types from stem cells. Breakthroughs like Melton's, Chien says, allow investigators to "envision the power that systems for redirecting cell development can have, from their use in modeling human disease, to the most elusive goal of all—personalized regenerative medicine."

What's Next? "Regenerative medicine is between acts, in an intermezzo period," says Chien. "We're moving from stem cell biology toward stem cell therapeutics. We'll no longer just insert cells into the heart and hope they go where we want and do what we want. Instead, I think we'll use pluripotent stem cells to make functioning 'heart parts' that we can simply put into place."



PHOTOS: DR. JONATHAN CLARKE/WELLCOME IMAGES (FAR LEFT); R. BICK AND B. POINDEXTER/SCIENCE PHOTO LIBRARY, UNIVERSITY OF TEXAS MEDICAL SCHOOL



IMAGES COURTESY OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION (ABOVE); COURTESY OF JANET WASA (FAR RIGHT)

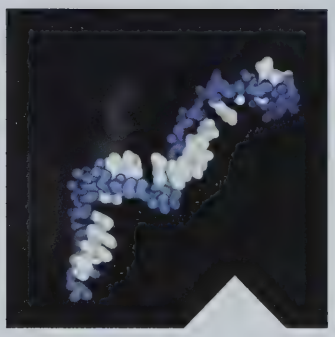
A New Generation of Antibiotics

Realm of Imagination: Is it possible to stem the population's growing resistance to antibiotics, to rescue the healing power of these medical workhorses? Does the door to discovery hinge only on finding new, broadly targeted bacteria-fighting agents or does it also open on ways to equip antibiotics with new tools to dismantle old foes?

From Shadow to Substance: "In the golden age of antibiotics," says Suzanne Walker, an HMS professor of microbiology and molecular genetics, "everyone wanted a broad-spectrum antibiotic—and they were not difficult to find." The deadly effectiveness of those drugs is waning, and scientists like Walker now search for new ways to fight pathogenic bacteria. Increasingly, investigators seek points of weakness in individual species, such as *Staphylococcus aureus* and other "superbugs" that defy treatments. Walker's research has shown how one molecule, wall teichoic acid, ensures that *S. aureus* cells divide properly and form bacterial cell walls strong enough to withstand hostile environments. Walker's work may lead to modifications of potential antibiotics to interfere with bacterial cell wall assembly. Imaging advances have also assisted the search for novel ways to defeat pathogenic bacteria. Fluorescent imaging can now follow a bacterium as it lives and dies, revealing how and when antibiotics kill the invader by compromising cell membranes.

The Harvard Dimension: State-of-the-art facilities, such as the School's Institute for Chemistry and Cell Biology, allow Walker and others to screen antibiotics for their ability to disrupt bacterial biosynthetic pathways. A federally funded project on antibiotic-resistant infections headed by Michael Gilmore, the Charles L. Schepens Professor of Ophthalmology at HMS, is focusing Harvard's research talent on new ways to fight pathogenic bacteria.

What's Next? "We will learn more about the life and death of bacteria," says Walker, "so that we may exploit pathways key to bacterial survival. And we need to learn how to prevent bacteria from transmitting resistance."



The Many Roles of RNA

Realm of Imagination: What happens when a research project becomes a prism through which researchers can view anew the fundamental cellular processes of transcription and translation? They might just find that RNA, long a comfortable character actor in that gene–protein drama, assumes many guises and may even hold a principal role.

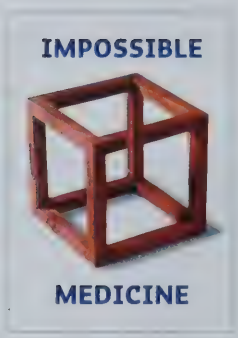
From Shadow to Substance: The discovery of small RNAs likely resulted from such a prismatic view. These tiny molecules regulate the production of thousands of proteins in plants and animals. Pinpointing their roles was aided by new tools for sequencing large amounts of DNA. "With this technology," says Gary Ruvkun, an HMS professor of genetics at Massachusetts General Hospital, "we could suddenly see all the genes of several organisms." Ruvkun used the nematode *Caenorhabditis elegans* to isolate *let7*, one of the first microRNAs. Ruvkun found *let7* to be pivotal to *C. elegans*' development; he also discovered it within the genomes of other organisms. This clue meant that small RNAs were conserved over eons and species, making the molecules candidates for treating gene-based diseases.

The Harvard Dimension: Research on small RNAs has benefited a large fraction of studies at HMS, says Ruvkun. Clinical research by Judy Lieberman '81, an HMS professor of pediatrics at Children's Hospital Boston, found RNA interference, or RNAi, disabled genes that transmit the herpes simplex virus type 2. Other work, co-led by Louis Kunkel, also an HMS professor of pediatrics at Children's, looks to microRNAs to treat muscular disorders.

What's Next? "Small RNA research has two great thrusts," says Ruvkun. "One is its use as a technical tool, and the other is its interesting biology. Many researchers use RNA as a tool, and their work is revolutionizing how laboratory biology is done. But the real revolution will occur when scientists discover why RNAi works so well, what processes it's mediating, and what it's doing in organisms. These investigations eventually will lead to the successful use of RNAi in medicine."







Trading Spaces

Leaders in medical research can enrich their creative output by moving between industry and academia

MEDICAL RESEARCHERS have long navigated an uneasy course between industry and academe. Recently, with attention increasingly placed on issues of conflict of interest, the pressure has grown to attenuate if not break ties between the two. But unique truths lie in the boundary waters; here, four leaders from the Harvard Medical School community share what they've learned charting careers that cross the lines.



Phyllis Gardner, MD

PROFESSOR OF INTERNAL MEDICINE AND CLINICAL PHARMACOLOGY
STANFORD UNIVERSITY SCHOOL OF MEDICINE

"Physicians and scientists approach discovery in just the opposite way—we identify problems and determine how to fix them."

Joining discovery with entrepreneurship. For many physicians, a career in medicine is a straight line—an orderly road that takes them from education and training to patient care, teaching, or a corporate position. Fewer pursue a route that winds between the seemingly disparate worlds of academia and biotech. That's the path Phyllis Gardner '76 has trod.

"I've spent much of my career in academics, research, industry, or some combination of the three," says Gardner, now both a professor of internal medicine and clinical pharmacology at Stanford University's School of Medicine and a partner at Essex Woodlands, a California-based health care venture capital and growth equity firm. "Each of these experiences has helped inform the others."

Clinical care. Laboratory research. Consulting gigs. A deanship. While at first glance, Gardner's professional life seems like a whirlwind sampling of all facets of medicine—her rapid, matter-of-fact recounting of her lengthy resume leaves the listener breathless—it is in truth a logical progression for a physician drawn to the most enriching aspects of all those fields.

Gardner's professional journey began at Stanford, where she ran a laboratory focused on cell biology and ion-channel biophysics and worked in a cardiac arrhythmia clinic. After more than a decade in academia, though, she found herself drawn to the private sector and took the position of vice president of research at the ALZA Technology Institute, a drug-delivery systems company. Eventually she returned to Stanford, where she worked as a professor and, briefly, as dean of education, while still consulting for ALZA and then other corporate ventures. The motivation for constant change was simple for Gardner, who has always been driven by curiosity. "I found all of these opportunities interesting," she says, "and felt I had something to offer them in return."

What she has offered industry and academia is the perspective gained from her experiences in both. "Engineers tend to invent a widget and then figure out the best use for it," she explains. "But physicians and scientists approach discovery in just the opposite way—we identify problems and determine how to fix them. That's what I've been able to bring to my work in industry."

Likewise, Gardner says, her experience in the for-profit world has enhanced her academic life, particularly in her role as student advisor. "Stanford has an entrepreneurial student body—remember, not everyone in medical school wants to go into patient care," she says. "Because I've worn so many career hats, I can be a role model for students who don't necessarily plan to enter clinical work."

At a time when concerns about conflicts of interest are making headlines, Gardner's varied career shows how academia and industry can benefit one another. "I certainly understand how the interaction between these fields can be problematic," she says. "When physicians accept direct fees to promote clinical trials, for example, there's no way that doesn't influence how they make decisions for their patients." At the same time, she believes that when doctors work or consult for industry and for a university, the results can be positive for all involved.

"My biggest loyalty is always to my students," she says. "And to be able to share my experiences with them has been incredibly rewarding."

—*Jessica Cerretani*

Setting priorities by patient need and scientific impact. When the call came, Mark Fishman '76 was at his desk, dispatching his administrative duties as chief of cardiology at Massachusetts General Hospital—something, he recalls, involving reimbursement and the cath lab.

On the line was Daniel Vasella, chief executive of Novartis. The two men had never met, but Vasella wanted Fishman to lead global research for the Swiss drug maker. Fishman was flattered but perplexed. In 2001, Fishman was an HMS professor of medicine well known for pioneering zebrafish models to explore the genetics of organ development. But he'd never developed a drug; in fact, unlike many peers, he'd never even consulted with a drug maker.

"I didn't even know Novartis *was* a drug company," Fishman says. (In fact, it's one of the world's largest.)

Fishman agreed to dinner—and the two physicians hit it off. Although Fishman declined to join Novartis, he offered to provide unpaid advice as Vasella reassessed the company's approach to research. During the ensuing six months, he counseled company leaders to separate research from marketing and to relocate their scientific headquarters to the United States.

Novartis agreed to the changes, and again Vasella inquired about Fishman's interest in the job.

"I said no, I wasn't negotiating," Fishman recalls. "I was just trying to be helpful."

But Vasella proved persuasive. In 2002, Fishman accepted the job of president of the new Novartis Institutes for BioMedical Research and fleshed out his sketch of an independent, global research organization headquartered in Cambridge, Massachusetts. His strategy: identify priorities by individual patient need—regardless of population size—and by scientists' ability to make an impact. It was a radical departure in an industry that based decisions on estimates of a drug's value long before it reached the clinic.

"Historically, the pharmaceutical industry has been terrible at predicting what something would be worth," Fishman says, pointing to forecasts that cholesterol-lowering statins would earn $50 million a year globally. (At their peak in 2006, U.S. sales alone neared $20 billion.) Yet executives wanted metrics. "That's just not how science works," he says.

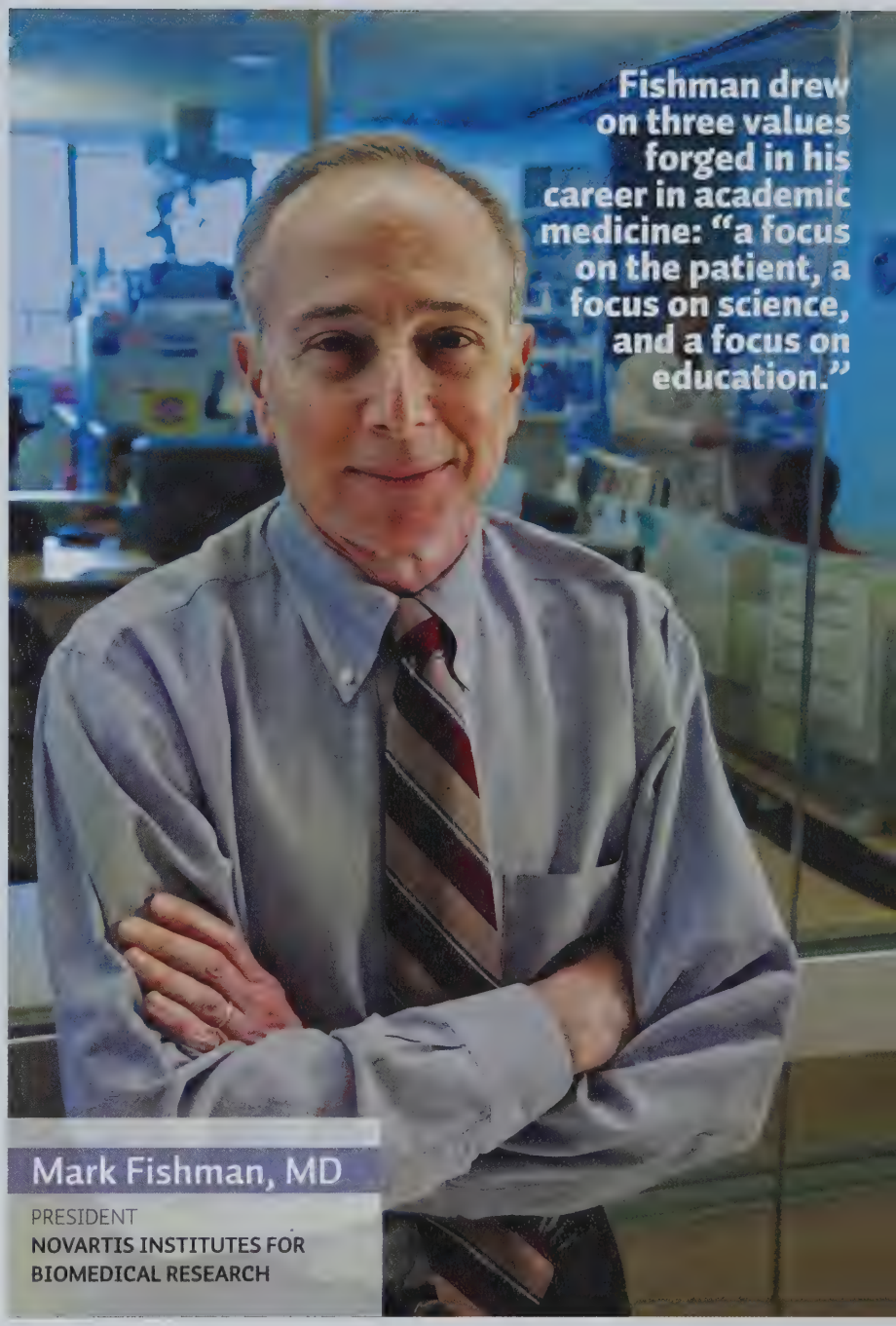
To enact the profound changes that his strategy entailed—shuttering some programs and launching others—Fishman drew on three values forged in his career in academic medicine: "a focus on the patient, a focus on science, and a focus on education." The last proved critical in transforming the culture of the organization.

It's a recognizable culture. "The personalities and the body piercings don't differ from those in academia," Fishman says. What's exciting, he says, is the sense of destination. "At Novartis, the enthusiasm explodes when we get our first positive result with a patient," he says. "It's amazing to hear that someone's cancer has gone away when nothing else worked, or that a kid has stopped having seizures."

At such moments, a hush falls over the room, Fishman says. Then, Novartis scientists will break out in applause—or, in the European style, pound the table.

That, he didn't change.

—R. Alan Leo





Joan Brugge, MD

CHAIR
DEPARTMENT OF CELL BIOLOGY
HARVARD MEDICAL SCHOOL

At the biotech company, she set the research agenda for senior scientists; as a department chair, she stays out of the way.

Placing a premium on understanding people.
At least some of her audience was awake.

It was 1997, and Joan Brugge was giving the pitch, one of 17 identical presentations over five days in Japan, one trip of many to drum up investment in ARIAD, the Cambridge, Massachusetts, biotech firm where Brugge had served as senior vice president and director of research since its celebrated founding in 1992. ARIAD's mission, Brugge told room after room of scientists and potential investors, was to identify and develop novel cancer therapies through structure-based drug design focused on protein–protein interactions. Good drugs built on good science. But while research was uncovering promising candidates, the hard work of developing them into drugs had begun to pull focus away from the discovery of new targets.

So increasingly, Brugge found herself on the road, an evangelist in an age of evangelists, touting a scientific effort from which she was increasingly removed, and which was itself increasingly removed from discovery.

It was around that time that Brugge, a former Howard Hughes Medical Institute investigator and professor at the University of Pennsylvania, saw two paths before her. "I had to choose between becoming a full-time manager at a higher level or returning to academic research," she recalls. "I knew which I loved."

So that year, Brugge accepted a professorship in Harvard Medical School's Department of Cell Biology. Once again the head of her own laboratory, Brugge would spearhead fundamental advances in cancer research, including the development of three-dimensional tissue cultures to better model breast cancer and other tumors. And when she agreed to chair the department, in 2004, she found that her experience in industry would serve her well.

"I learned a lot about leadership when I was at ARIAD," Brugge says. Some lessons weren't applicable: At the biotech company, she set the research agenda for senior scientists; as a department chair, she stays out of the way. "My role is to create fertile ground for discovery," she says. Part of that is fostering collaboration.

A story from her ARIAD days makes the point. When a promising compound showed efficacy in cell-based assays, a biologist wanted evidence that it was working through the intended mechanism. But when Brugge asked a chemist to design a control, she found herself caught in a cultural divide. Whereas biologists deal in observation and uncertainty, chemists dwell in an orderly house of mechanistic determinism. "Controls," the chemist replied, "are for losers."

Today, Brugge invokes that anecdote for her students. The most important ingredient to a successful collaboration, she tells them, is understanding the perspectives of other people. Indeed, it is lessons about people, Brugge says, that have most helped her as a leader.

What advice would Brugge give a rising scientist, weighing a career in industry or academe? "I would encourage them to try to get to know themselves as much as possible," she says. "Do they prefer to function as individuals or as part of a team?" But sometimes, the difference is less than meets the eye. "Everyone who directs a lab," she says, "is a CEO of his or her own little company."

—R. Alan Leo

"How do you work in a way that honors the principles and the mission of the academy, yet helps the academy realize its translational goals?"



Michael Rosenblatt, MD
EXECUTIVE VICE PRESIDENT AND CHIEF MEDICAL OFFICER
MERCK & CO.

Supporting the physician–scientist's role. When he graduated from Harvard Medical School, Michael Rosenblatt '73 imagined he would spend a career in academic medicine. He had just collected the Soma Weiss Award for best student research and would soon rise from trainee to chief of the endocrine unit at Massachusetts General Hospital. But a decade later, his groundbreaking research on parathyroid hormone led to a consulting role with Merck & Co.—and to new imaginings.

"All the things I was writing in grant proposals about how my research eventually would lead to new treatments—well, Merck scientists were doing it," Rosenblatt says. He was also struck by *how* they were doing it: together, sails filled with the kind of collaboration that the academic crosswinds of grant writing, publication, and tenure too often countervail.

So in 1983, Rosenblatt accepted a position as vice president for biological research at Merck Research Laboratories, where he co-led development of a new treatment for osteoporosis. Approved in 1995, alendronate, better known as Fosamax, heralded a new generation of bisphosphonates that would transform treatment and prevention of osteoporosis.

"That was a success story that's had impact," Rosenblatt says. "It has spared fractures and saved many lives; I'm very proud."

Harvard came knocking again. In 1992, Daniel Tosteson '48, then dean of HMS, recruited Rosenblatt to lead the Harvard–MIT Division of Health Sciences and Technology. Here was an opportunity for Rosenblatt to give back—to develop the next generation of physician–scientists, even as he reconnected with his passion for research.

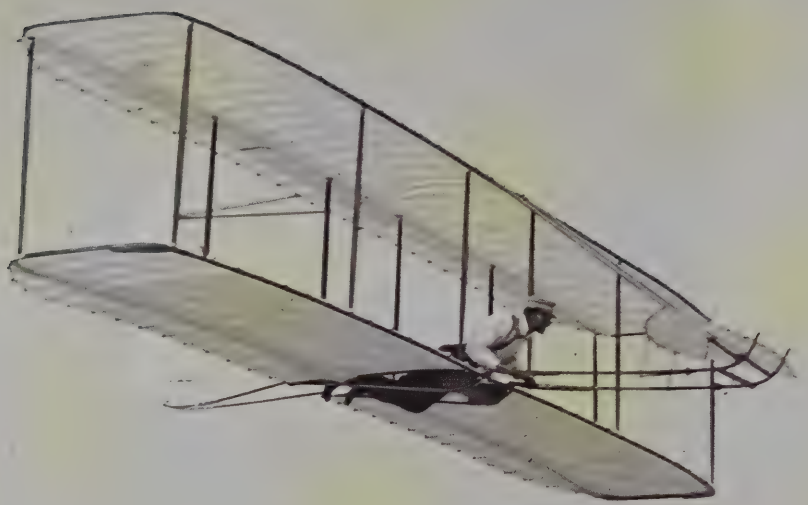
"Physician–scientists have a special perspective," Rosenblatt says. "To see a clinical problem, move to the laboratory, and then carry solutions back to the patient gives them a lot of insight."

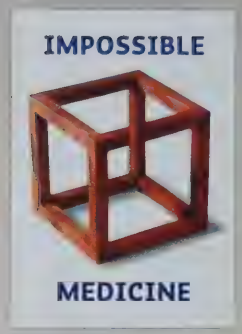
His next turn at academic leadership included the presidency of Beth Israel Deaconess Medical Center and later the deanship of Tufts University School of Medicine, where Rosenblatt drew on his experience to craft new policies governing conflicts of interest. "I was constantly grappling with the issue," he says. "How do you work in a way that honors the principles and the mission of the academy, yet helps the academy realize its translational goals?"

Now back at Merck, Rosenblatt is still grappling. As executive vice president and chief medical officer, the company's primary voice to the global medical community, he says research integrity demands clear rules, but he cautions that some policies chill collaboration—at a cost to science. Regardless of merit, he says, industry scientists are often excluded from the key committees of professional societies, and some societies have even considered preventing them from presenting their own data. Rosenblatt rattles off a list of Nobel laureates: Sir James Black, who developed beta-blockers; Gertrude Elion and George Hitchings, whose research produced numerous drugs, including the HIV drug AZT; and Godfrey Hounsfield, inventor of the CT scanner. All made their discoveries while in industry.

"I feel strongly that the medical profession should stand by its principles of openness and discourse," Rosenblatt says. "Advances in science should be judged on their quality and value, and not the institutional address of the researcher."

—*R. Alan Leo*





They All Laughed

Harvard doctors have a long tradition of earning the last laugh by persevering in the face of skepticism

by JESSICA CERRETANI

HISTORY IS FILLED with ill-fated schemes, from tailor Franz Reichelt's 1912 jump from the Eiffel Tower to test his "coat parachute"—it failed—to Ford's four-wheeled flop, the Edsel. Other innovators and theorists, though mocked in their day, have eventually been proved correct. The world, it turns out, is indeed round. ■ Medicine is no different. For every instance of bloodletting, lobotomy, and snake elixir, other ideas have changed human health for the better. These four Harvard Medical School physicians defied skepticism to bring us lifesaving discoveries. As the Gershwin tune concludes, "Who's got the last laugh now?"

PHOTO: COURTESY OF THE LIBRARY OF CONGRESS



IMAGE: REDWOOD LIBRARY AND ATHENAEUM, NEWPORT, RHODE ISLAND, BEQUEST OF LOUISA LEE WATERHOUSE (MRS. BENJAMIN WATERHOUSE) OF CAMBRIDGE, MASSACHUSETTS. DIGITIZED AT THE NATIONAL GALLERY OF ART

SHOT IN THE ARM: Fascinated by reports that British physician Edward Jenner had developed a vaccine effective against cowpox, Benjamin Waterhouse set out to test its effectiveness against smallpox—using his young son as subject. The test, and subsequent ones, proved successful, spurring Waterhouse to a lifetime as an advocate of vaccination.

Benjamin Waterhouse

These days, smallpox is little more than an unpleasant memory, but for millennia, it was a scourge that felled millions of people around the world, permanently disfiguring those who survived. By 1798, British physician Edward Jenner had developed a vaccine that used cowpox, a related disease, to protect against smallpox. Despite his success in England, the vaccine was ignored in the United States.

Enter Benjamin Waterhouse. A founding faculty member of Harvard Medical School and its first Professor of Theory and Practice of Physic, Waterhouse had been educated in Europe and kept in touch with a London physician, who sent him Jenner's report on the vaccine's effectiveness. Intrigued, Waterhouse began a correspondence with Jenner and soon convinced him to send samples of the vaccine. Then, in a display of either an overwhelming faith in Jenner's work or an arrogant overconfidence in his own judgment, Waterhouse carried out the first tests of the vaccine—on his five-year-old son.

Fortunately for both elder and younger Waterhouse, the vaccine worked. Encouraged, the good doctor inoculated several other relatives to, he later wrote, "convince the faithless and silence the mischievous." In the summer of 1800, he inoculated a twelve-year-old servant before delivering him to a Brookline, Massachusetts, smallpox hospital, where he would undoubtedly be exposed to the disease. The boy remained healthy, although he did report a sore arm from the needle jab. (The doctor's ego, too, was unharmed. Of his work, he later wrote, "I attained a triumph so complete that it is now rare to meet an American with marks of smallpox on his face....Vaccination saves millions of lives every century, like the blessing of the sun, universal and everlasting.")

Waterhouse advocated for smallpox vaccination throughout his life, enlisting the help of then-president Thomas Jefferson. Yet his efforts were met with resistance. Critics declared the vaccine ineffective, probably the result of poor sanitation and lack of refrigeration. Or perhaps it was jealousy: Some envied Waterhouse's European medical training and ascribed to him a condescending demeanor. Indeed, the doctor engaged in feuds with the Boston medical establishment, including another founding faculty member of HMS, Professor of Anatomy and Surgery John Warren. A sticking point was Waterhouse's refusal to share the vaccine with many local physicians—and his demand for part of the profits when he did share it. Whether this was an attempt to ensure proper inoculation or to create a monopoly remains unclear.

Eventually, thanks in part to—and perhaps in spite of—Waterhouse's actions, smallpox vaccination became widespread. By 1897, barely half a century after his death, the disease had been virtually eliminated from the United States; in 1979, the World Health Organization certified the disease's eradication. A plaque on his grave credits Waterhouse for his work in vaccination and his success in overcoming "popular prejudice and distrust...[to earn] the gratitude of future ages."

Oliver Wendell Holmes, Sr.

Oliver Wendell Holmes, Sr. is perhaps best known as a poet, but his greatest masterpiece involved infection, not inflection. While an undergraduate at Harvard, Holmes began writing as a hobby; the year after his graduation, the publication of his poem "Old Ironsides" brought him national attention—and helped generate public support to preserve the USS *Constitution*. Soon after his graduation, he enrolled in medical school, earning his degree from HMS in 1836.

Holmes had long been a critic of the state of medicine: He railed against the practice of bloodletting as ineffective, denounced homeopathy as "the pretend science," and decreed that if all current medications "could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes." At the same time, he sought to improve the conditions under which physicians worked—and under which too many patients perished. Yet his attempts at reform were highly controversial. His theory was, after all, based on the blasphemous claim that doctors were killing their own patients.

In 1843, Holmes published his essay "The Contagiousness of Puerperal Fever." It did not meet with the same warm reception as "Old Ironsides." In fact, the essay—in which Holmes maintained that puerperal fever, a common cause of maternal death during childbirth, was a transmissible disease—was met with skepticism. Two prominent obstetricians, Hugh Hodge and Charles Meigs, attacked Holmes's theory, as did the doctor's former HMS instructor, Walter Channing. Although their resistance seems outlandish today, Holmes's essay predated Louis Pasteur's experiments with bacteria and the germ theory of disease. Because puerperal fever didn't affect every patient exposed to it, critics argued, it could not be contagious.

Holmes was undaunted. He collected evidence of doctor-to-patient transmission of puerperal fever, suggesting that physicians spread the disease through the blood and other body fluids that caked the very clothing they wore. In 1855, with an HMS deanship under his belt, Holmes reprinted his essay, pointedly addressing his critics in the preface: "I had rather rescue one mother from being poisoned by her attendant, than claim to have saved forty out of fifty patients to whom I had carried the disease." This time, as medical opinion had begun to evolve, the essay garnered positive attention. Today, Holmes's greatest legacy lies not in a poetry anthology, but in his success in advancing the concept of infectious disease—and in allowing most women to give birth without the fear of dying.

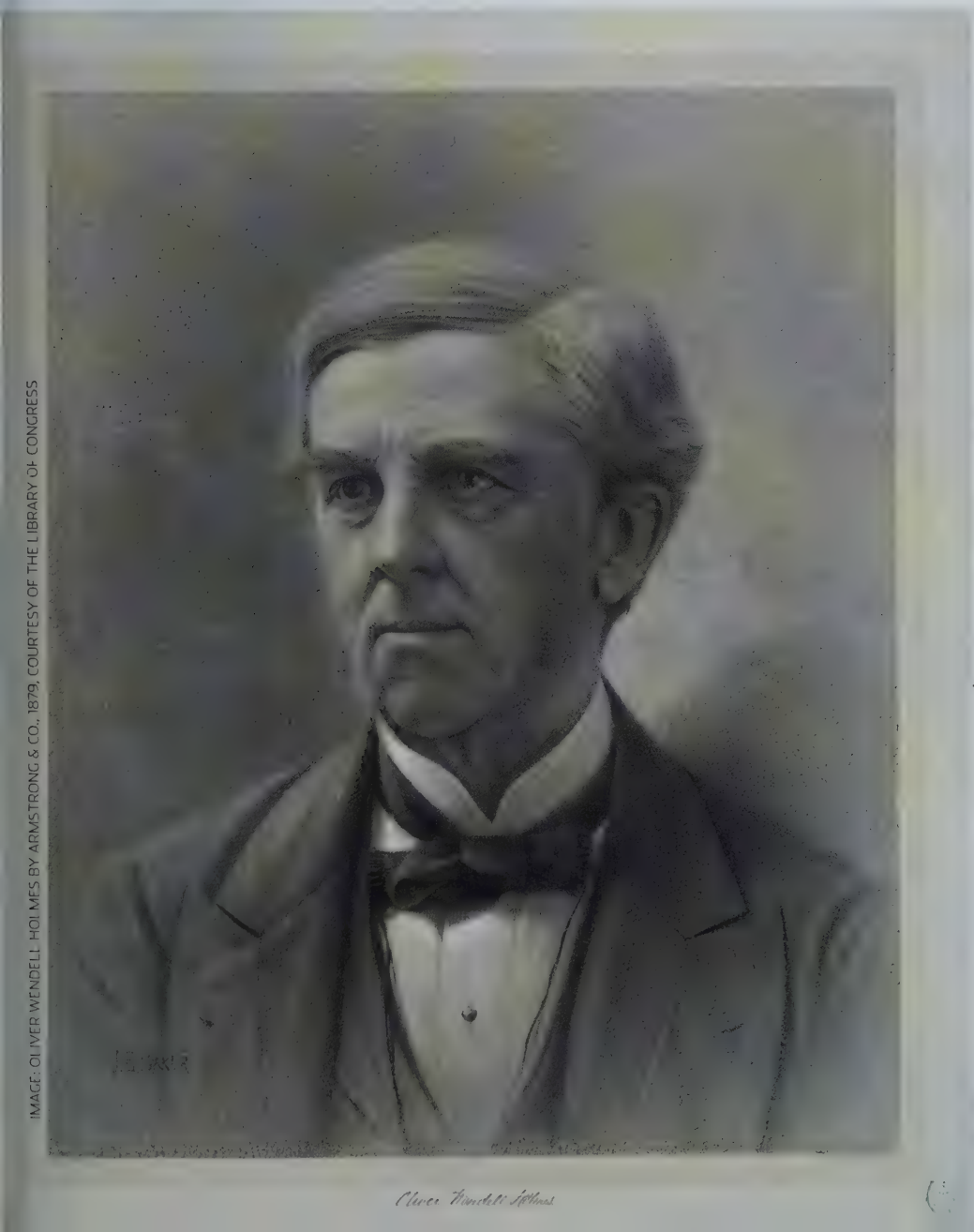


IMAGE: OLIVER WENDELL HOLMES BY ARMSTRONG & CO., 1879, COURTESY OF THE LIBRARY OF CONGRESS

CLOTHES ENCOUNTERS: Well before the germ theory of disease was posited, Oliver Wendell Holmes, Sr., proposed that puerperal fever, a common cause of maternal death during childbirth, was spread by doctors who failed to properly wash their hands or change their blood- and fluid-encrusted garments before tending to women in labor.



PHOTO: COURTESY OF THE ALBERT AND MARY LASKER FOUNDATION

JOLT OF RECOGNITION: From his design of the implantable artificial pacemaker, to his development of the heart monitor, to his crafting of a device that corrects the erratic actions of a defibrillating heart, Paul Zoll's imagination was heart-centric, a focus that has since improved millions of lives each year.



PHOTO: MARK OSTOW, COURTESY OF CHILDREN'S HOSPITAL BOSTON

Paul Zoll

Before the 1950s, the most effective way to get a stopped heart beating again was both crude and dangerous: Cut open the patient's chest, grab the heart, and squeeze. Cardiologist Paul Zoll sought a better approach—one that kept the patient's torso intact and the physician's hands relatively clean. That his method was met with horror by some is merely a testament to its stunning effectiveness.

A 1936 graduate of HMS, Zoll was working as a U.S. Army doctor during World War II when he watched a colleague remove shrapnel from a patient's beating heart. Amazed by the organ's responsiveness to outside contact—in this case, from a scalpel—he began brainstorming less invasive ways to stimulate the heart.

Zoll was not the first to hope for such a solution. In 1930, cardiologist Albert Hyman, Class of 1918, had designed a machine powered by a hand crank that produced electricity. When delivered through a needle plunged into a heart, the electricity triggered beats from the stalled organ. Yet the medical community had paid this invention little heed.

Two decades later, Zoll began work on a kinder, gentler alternative: a so-called external pacemaker that relied on an electrical current outside the chest cavity to stimulate the heart. By 1952, Zoll had published studies of his creation, noting its ability to resuscitate patients in cardiac arrest. While his first patient lived just 20 minutes, another survived for 11 months following 52 hours of pacemaker stimulation.

It should have been a slam dunk. Instead, Zoll's innovation met with a frustrating combination of physician resistance, blocked funding, and public outcry. The pacemaker, scoffed one of his colleagues, was "a toy." Zoll was initially denied a grant by the U.S. Public Health Service, possibly because the head of the award committee had failed at similar research years earlier. And religious groups described the pacemaker as tampering with God's will. The media did Zoll no favors. "Dead Brought Back to Life!" screamed one local paper's headline. "Many people," Zoll later wrote, "thought that it might be blasphemous, improper, or unethical to keep a patient alive by such artificial means."

Undeterred by sour grapes and superstition, Zoll went on to develop the first defibrillator and heart monitor. Because he neglected to patent his creations, Zoll saw others—including fellow HMS graduate Judah Folkman '57—refine the technology until small, implantable pacemakers became the norm. At the time of Zoll's death in 1999, an estimated half million new pacemakers were being implanted in patients annually, saving countless lives.



SEE, DO, TEACH: The success that Judah Folkman achieved in the late 1990s came after decades of dogged observation and investigation. When Folkman proved the concept behind his angiogenesis theory, the doors to innovation flew open as he and others sought ways to disable a tumor's ability to spur the growth of nourishing blood vessels.

Judah Folkman

Judah Folkman '57 became a reluctant celebrity in 1998, when a front-page *New York Times* article quoted a colleague as declaring, "Judah is going to cure cancer in two years." Hyperbole aside, the statement did little to acknowledge Folkman's long struggle to prove his theory that a cancerous tumor's growth could be halted by choking off its blood supply.

The face of cancer treatment began to change in the early 1960s, when Folkman, then at the National Naval Medical Center, noticed something curious about the tumors he was studying in the lab: They all grew to a certain size—and then stopped growing altogether. The common link, he realized, was the eventual inadequacy of their blood supply. It seemed simple, perhaps too simple. A "successful" tumor, Folkman suspected, must somehow be able to induce new vessels to grow within it, a process called angiogenesis. Disable that mechanism, and you could potentially starve the malignancy. And yet, as Folkman later admitted, "I didn't have any idea that it would be some 30 years to try to understand the process."

In 1971, Folkman published his first major study of angiogenesis in *The New England Journal of Medicine*, arguing that the process enables tiny clusters of malignant cells to become larger metastatic growths. The response was tepid at best. Folkman reported seeing researchers "laughing in the corner" when he spoke at conferences. His friend John Enders, an HMS professor who had shared the Nobel Prize for his work on the poliovirus, warned him that he would likely need to conduct dozens of experiments before he could convince the skeptics. It took hundreds.

By the end of the 1980s, those experiments—as well as scientists' discovery of the trigger for angiogenesis, vascular endothelial growth factor, or VEGF—had begun to turn the tide. The *Times*' bold prediction, of course, did not come to pass. Yet Folkman, who was the Julia Dykman Andrus Professor of Pediatric Surgery at Children's Hospital Boston at the time of his death in 2008, left an encouraging legacy: The anti-angiogenesis drugs his research inspired have restored vision in people with age-related macular degeneration and other eye diseases.

Jessica Cerretani, a former assistant editor of Harvard Medicine, *is now a full-time freelance writer.*

ASSEMBLY INSTRUCTIONS
HOW TO BUILD A BETTER HEALTH CARE DELIVERY MODEL

WHEN IT COMES TO DELIVERING health care in this country, everyone, it seems, has an opinion. While many argue over the way we pay for health care, Timothy Ferris '92, an HMS associate professor of medicine and medical director of the Mass General Physicians Organization at Massachusetts General Hospital, has taken a different approach. "The question shouldn't just be *how* we pay for health care," he says, "but what we can do to lower payments while enhancing care."

To those ends, Ferris works to implement an array of delivery-systems changes at Mass General with the goal of improving outcomes and decreasing costs. One of these is the Mass General Care Management Program's Medicare Demonstration Project, which identifies ways to reduce the cost of care for the sickest 15 percent of Medicare beneficiaries, who account for about 75 percent of health care costs. The goal: to help those patients achieve better health and, consequently, use fewer resources. Data suggest that these approaches to curbing health care spending can decrease not only inpatient and emergency department admissions, but also hospital readmissions.

—*Jessica Cerretani*

3 Reduce readmissions.
High-risk patients who can't (or won't) take care of themselves are often readmitted to the hospital within weeks of being released. Hospitals should reach out to those patients to help them transition home and avoid setbacks.

2 Design each episode of care.
Ensure that each particular treatment is needed. Does the patient really need a hip replacement, for example, or could other therapies avoid or delay it? If treatment *is* necessary, consider all the steps involved. What tests and therapies do you need before performing that operation? There are often literally thousands of options, but only a few may be warranted for a particular patient.

1 Determine which patients are at highest risk.
Review electronic health records to identify those who are sickest, whose chronic conditions are poorly managed, who take multiple medications, and who make frequent visits to emergency departments. Focus your efforts on this group.



ILLUSTRATION: WESLEY BEDROSIAN

5 Get technical.

Technology can help physicians manage patients' care. Virtual visits by phone or through Skype or email can replace unnecessary—and costly—appointments. Web-based portals can allow patients to view their health records, request appointments, renew prescriptions, and accomplish other tasks that consume caregivers' time. And computerized decision-support programs can alert physicians to a patient's allergies, potential drug interactions, and other issues that help guide treatment choices.

4 Offer alternatives.

Many patients visit the emergency department for non-emergencies, such as sore throats and ear infections. By extending the hours of urgent-care clinics, hospitals can avoid misuse of emergency departments, further cutting costs.

6 Work with patients.

Patients should have a say in their care. Caregivers should discuss the risks and benefits of treatment—and of no treatment—with every patient *before* delivering care.



7 Work as part of a team.

Everyone caring for a patient should follow the same plan. Caregivers need to carve out time to assess how they can better support each other, best use the skills of all team members, and continuously improve what they do.

8 Track performance.

By documenting the outcomes of particular treatments as well as the costs of the care, hospitals can assess effectiveness and efficiency, helping physicians choose the best therapies for their patients.



MARVELS OF ENGINEERING: After severe frostbite in a mountaineering mishap led to amputations when he was a teen, Hugh Herr became interested in prosthetic engineering. He is now the holder or co-holder of more than a dozen patents related to assistive devices, including those for a computer-controlled artificial knee, an ankle–foot orthosis, and the world's first powered ankle–foot prosthesis.

SMART SCIENCE

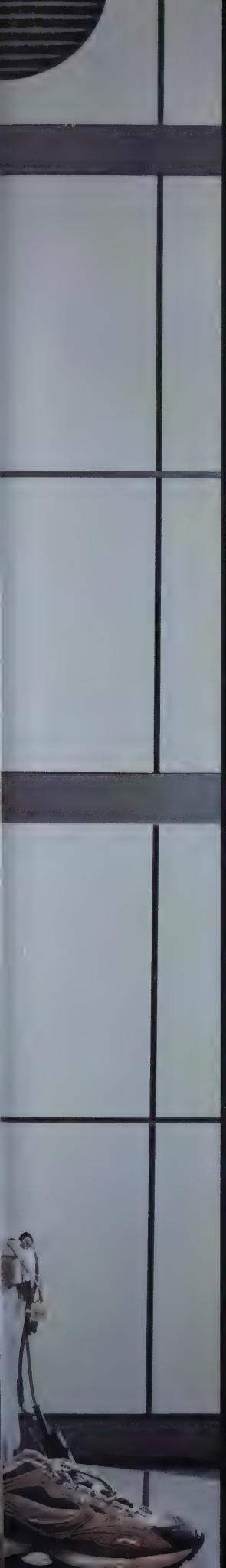


PHOTO: SHAWN C. HENRY

Fancy Footwork

SUPPOSE YOU MET AN AMERICAN who had lost a leg. What would your best guess be as to the reason for that loss?

If you were to say an explosive device in Iraq or Afghanistan, there's a chance, not quite 1 in 1,000, that you'd be right.

A motorcycle accident or other trauma? Better odds: 7 in 100.

Diabetes? Bingo.

More than 8 in 10 of the 1.7 million Americans who have lost a limb—usually a leg or foot—have done so to dysvascular disease, mainly the result of diabetes. So despite advances in care that have reduced amputations for all other causes, researchers expect the number of Americans affected to double by 2050, lifted almost entirely on the storm tide of obesity and its complications.

But it's that first group—the 1 in 1,000 who lost a limb in service to their country—that has accelerated the development of high-tech prostheses. In the past decade, defense agencies have funded research that is now yielding a new class of wearable robotics. Used today by a handful of war veterans, these prostheses will soon be available to the other 99.9 percent of those who have lost a limb.

At the vanguard of the smart prosthesis revolution is Hugh Herr, an HMS lecturer on physical medicine and rehabilitation and an MIT associate professor in the Harvard–MIT Division of Health Sciences and Technology. Herr, who underwent a double amputation in 1982, has developed the first ankle–foot prosthesis that, according to key measures, works as well as a natural foot. About a dozen people, including Herr and several veterans, have used the prototype, and this year his company, iWalk, will bring the PowerFoot BiOM (pronounced "bi-ohm") to the public. Here's how it works.

To propel a walker forward with each step, modern prostheses use flexible materials, such as carbon fiber, to store energy at impact and then release it. Powered limbs boost that passive propulsion with a motor. The most advanced allow the wearer to adjust power for, say, walking faster or striding uphill. Herr's engineered foot goes one further, building the adjustment decision-making into the prosthesis itself—just as a natural foot adjusts reflexively to changes in pace or incline.

That control relies on a dozen sensors that each gather about 250 data points per second, measuring the ankle–foot's force, torque, and absolute positions along three degrees of freedom. Five microprocessors crunch the data, adjusting to terrain in real time. "The device can recognize that a person is on a step, or on a slope between steps," Herr says. That information keeps the foot moving at a natural gait.

This biomimetic approach required basic research into the structure and function of the human foot. "Believe it or not, the science of how we move, how we walk, is not fully developed," Herr says. "So we developed biophysical models that walk to help us predict energies and torque." Neuromuscular modeling yielded insights about the human ankle, Achilles tendon, and calf, including a deeper understanding of the Golgi tendon organ, a proprioceptive, or self-sensing, organ at the intersection of muscle and tendon that helps control reflexive muscle action.

It's a short step from as good as nature to better, Herr says: "We're knocking on the door of augmentation." He points to three challenges to crossing that threshold, each a different example of an extreme interface. The first he calls dynamical: building an interface that behaves like a human limb. This is where the PowerFoot has advanced the most and could go further through improved sensors and pattern recognition. The second he calls mechanical: attaching the limb to a human body. The ideal prosthesis would attach directly to the skeleton, as natural limbs and prosthetic joints do now, but problems of infection arise when prostheses pierce the body. The third he calls electrical: controlling the limb through new types of brain–machine interfaces.

Society has already crossed one other important threshold, says Herr: the psychological. Not long ago, he says, most people who had lost a limb hid their prosthesis from the world. No longer. "If you go to Walter Reed Army Medical Center, soldiers don't want that beautiful titanium leg covered up," Herr says. "They wear shorts to the mall."

— R. Alan Leo

FIVE QUESTIONS FOR SANJIV CHOPRA



Sanjiv Chopra, MBBS, MACP

Roles: Professor of Medicine and Faculty Dean for Continuing Education, Harvard Medical School; Senior Consultant in Hepatology, Beth Israel Deaconess Medical Center

Latest Book: *Doctor Chopra Says: Medical Facts & Myths Everyone Should Know* (coauthored with Alan Lotvin; Thomas Dunne Books, 2010)

What inspired you to write *Doctor Chopra Says*?

We're barraged with information—and misinformation—about our health all the time. It's difficult for people to sort fact from fiction: One day we're told that coffee or vitamins are good for us; the next day we're told they aren't. Hundreds of new studies appear on various health issues nearly every day. Even doctors can't wade through them all or know every important detail. That's why my coauthor, Alan Lotvin, and I decided to write this book. We talked with patients, colleagues, and friends to come up with the most interesting and controversial health myths, and then set about researching 38 of them.

How might consumers avoid confusion and sift fact from hype?

The best piece of advice I can give is to delve further. Don't just read the headline. Newspapers, magazines, television, and websites all want to grab your attention with sexy or dramatic sound bites, but there's always more to the story. It's important to understand the basics about different types of studies and how they're conducted.

What's the most surprising health fact you discovered while researching the book?

One of my favorites involves coffee. There's been the perception that coffee is bad for us, and some research has linked its consumption to a higher risk of heart attacks, birth defects, and miscarriages. But most of the evidence is positive: Large studies suggest that drinking coffee regularly may protect us against a number of health problems, including type 2 diabetes and liver cirrhosis. As a hepatologist, I find that particularly intriguing and have started asking patients about their coffee consumption.

You talk about wanting people to live an "aced life." What does that mean?

As a teacher, I'm partial to mnemonics. So I came up with one to describe what I consider a healthy lifestyle. *A* is for alcohol (in moderation) and aspirin (a low dose daily, with a doctor's consent); *C* is for coffee; *E* is for exercise; *D* is for vitamin D_3, the only supplement I recommend; *L* is for laughter; *I* is for finding ways to go inward, such as meditating; *F* is for fish; and *E* is for empathy. And then I add, "Don't go nuts remembering this!" to remind them that eating a small quantity of nuts daily appears to increase one's lifespan by two years. These tenets are what I recommend to patients and what I practice myself.

Educating consumers is important, but what about physicians?

As the School's faculty dean for continuing education, I am privileged to develop courses with colleagues to educate doctors so that through their work, their patients can lead healthier, happier lives.

—Interview by Jessica Cerretani

PHOTO: ROSE LINCOLN/HARVARD NEWS OFFICE

President's Report



At our February meeting, Harvard Medical Alumni Council members discussed ways we could enhance graduates' ties with the School and with each other. To that end, we made several decisions:

We will base reunion invitations on entering classes rather than graduating ones, as half of all students now take more than four years to graduate.

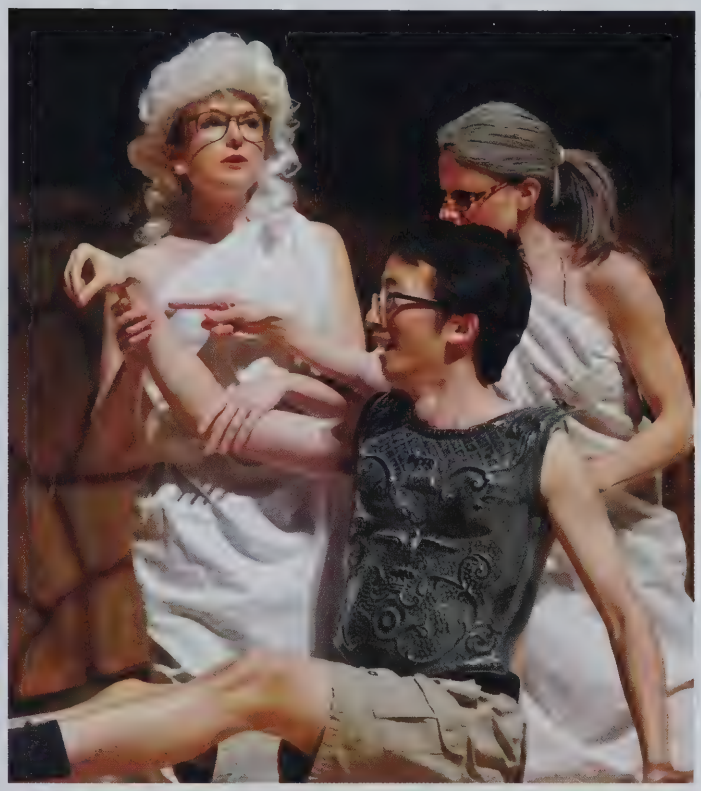
To broaden Council representation, we will propose to amend the Alumni Association constitution to create two new pentads, separating the now-combined 7th and 8th pentads, and splitting the "9th pentad and beyond" into the 9th pentad and the "10th pentad and beyond."

We will render the reunion books as downloadable electronic files, enabling both better access and cost savings.

Finally, we invite alumni around the world to offer solutions to complex health problems through Harvard Catalyst's ideation challenges (catalyst.harvard.edu).

We warmly welcome your feedback at hmsalum@hms.harvard.edu.

Gilbert Omenn '65 is a professor of internal medicine, human genetics, public health, and bioinformatics at the University of Michigan in Ann Arbor.



PHOTOS, FROM LEFT: COURTESY OF THE UNIVERSITY OF MICHIGAN; STEVE GILBERT

MAKE NO MISTAKE

The Second Year Show roasts its hosts

A high-achieving first-year HMS student has but one option when he receives a mediocre grade on an exam: travel back in time to make things right. At least, that's how it played out onstage during the Class of 2013's Second Year Show, *Marginal Past: Failure Is Not an Option.*

Loosely based on the film *Back to the Future*, the show centers on Bo, a first-year gunner who is sent reeling after receiving a "marginal pass" grade on his genetics exam. Finding little comfort in assurances that grades don't matter at HMS, Bo travels back in time with the assistance of the Ghost of Marginal Past, or GOMP, a nerdy student who also happens to have built a working time machine.

The time machine has glitches, however, and it whisks the pair through the ages, from the Garden of Eden to ancient Rome to a psychedelic party of the sixties. Wherever they travel, Bo and GOMP encounter younger versions of HMS faculty. Bo eventually learns to find balance in his life, but not before members of the HMS community get their traditional Second Year Show roasting.

Marginal Past cast its satiric net far and wide, with proper musical accompaniment. Dancing cadavers in the anatomy lab, for example, entertained with lyrics sung to the tune of "Stayin' Alive": "Well, you can tell by the way I've sold my soul/That I've lost my chance to unenroll/I'm Harvard property for good/It's been my dream since childhood."

Marginal Past included some musical standouts. Veronica Mitko nailed Lady Gaga in "Bad Bromance" ("I want your ugly genetic disease/Sequence your genome and I'll lower the fees/I want your genes/Genes, genes, genes, I want your genes"). Christian Strong, in portraying HMS Faculty Associate Dean for Student Affairs Alvin Poussaint, was notable not only for his vocal gifts in channeling Marvin Gaye in "Let's Get It On," but also for his superb comic timing.

The Class of 2013 further demonstrated talent through choreography and dance. In "September," a spoof on the Earth, Wind and Fire song of the same name, dancers revived bygone eras, with cavemen putting a primitive spin on the number alongside neon-clad movers and shakers straight from the eighties. And it wouldn't be the Second Year Show without a rousing Bhangra, the traditional Punjabi dance that closed this year's performance.

As is true each year, the breadth of musical and theatrical talent among the future doctors impressed. The most recent performance was such an enjoyable romp that one was left craving a Third Year Show.

—Emily Lieberman

CLASS NOTES

NEWS FROM ALUMNI



1943

Boris Bushueff

"My wife, Elizabeth Hunnewell, died two years ago. Fortunately, my four children live nearby—Elizabeth in Vermont, Paul on the Cape, Timothy and Catherine in New Hampshire. They take good care of me. I spend winters in New Hampshire and summers on the Cape. Everybody is welcome to visit."

1945

Giulio D'Angio

"I took several trips to medical meetings in 2010—some far (Sweden), some near (Boston). I was in Beantown twice and was much impressed by the improved Back Bay. HMS was unrecognizable with so much new construction. The same for Children's Hospital and Peter Bent Brigham."

John Packard

"I had a memoir published in the March/April 2010 issue of *Adirondack Life*. Pretty good for an 89-year-old!"

Stuart Quan

"I was fortunate enough to have celebrated the 25th anniversary of the Quan Fellowship in Neurobiology at HMS, concurrent with my 90th birthday. The celebration took place at the Northampton Country Club in Westhampton Beach, Long Island, on June 25, 2010. We heard from the HMS chair of neurobiology, Michael Greenberg, as well as from three of the Quan Fellows. They gave short talks in front of 140 family members, friends, and other guests at a festive luncheon. I am greatly indebted to my wife, Vicki, and to HMS."

1946

John Benson

received the Association of American Medical Colleges' Abraham Flexner Award for Distinguished Service to Medical Education. The award recognizes extraordinary individual contributions to medical schools and to the medical education community. In addition, the Institute of Medicine has named an anniversary fellowship in honor of Benson. The fellowship, sponsored by the American Board of Internal Medicine Foundation, will support early-career health scholars.

Milton Hamolsky

"Since my fourth 'retirement,' I've worked at Rhode Island Hospital, Brown's Albert Medical School, the Rhode Island Board of Medical Licensure and Discipline, and the Providence School Board. I'm currently on the Board of Governors at Lifespan Hospital System and the Board of Trustees at Home and Hospice Care of Rhode Island."

1947

Marvin Sleisenger

will receive the University Medal from the University of California, San Francisco, the highest honor the institution bestows upon its faculty. He is being recognized for his leadership in transforming the San Francisco Veterans Administration Medical Center into an academic medical center and a fully integrated part of the university.

1948

John Connolly

"I'm still enjoying good health, so I continue to work in my 45th year as a professor of surgery at the University of California, Irvine, where I was founding chair of the Department of Surgery."

1949

Henry S. Harvey

"I'm still married to Marjorie (68 years) and still living in an enclave in the former Prouty estate in the center of Littleton, Massachusetts. My son lives next door. A fool's paradise, perhaps."

1950

Renee Gelman

"Our 60th med school reunion was a great success. We look forward to our 65th!"

1953

German Malaret

"I'm retired from the practice of medicine, but I'm still active in the hearings and appeals section of the

PHOTOS: JAN REISS



Social Security Administration. I'm also doing expert witness work in malpractice claims, and I'm still working toward making Puerto Rico the 51st state of the Union. We lost our son last year to ALS."

1954

Richard Cattell

"We will be moving from our home of 53 years in the foothills west of Denver to a full-service retirement community in Manhattan, Kansas, by June 2011. Our son and Kansas State University are two miles away."

Charlotte Neumann

"I am still at the University of California, Los Angeles, schools of Public Health and Medicine, where I have been for more than 40 years, although I formally retired last July. I continue to commute to East Africa (mainly Kenya) to carry out nutrition intervention studies, mainly with women and children. I received several honors this past year, including entering the ranks of the 'Living Legends,' for International Union of Nutritional Sciences members who have reached the grand age of 80 and are still professionally productive. I also received the Nevin Scrimshaw Award for my contributions to nutrition research infrastructure building and training in Africa. My husband and I very much enjoyed our 55th class reunion, despite the low turnout. It was sad to learn how many are no longer with us. See you in 2014!"

John Peters

"I assume more and more of my classmates are retiring. I wish they would write about their activities at this stage of their lives. I do some selective reading in the history of science, mostly physics, and in the biographies of scientists, including Darwin, Freud, and many physicists."

1955

Paul Steinman

"Sandy and I continue to enjoy the Bay Area. I'm creaky yet busy with classes, theater, and travel. I'm still working part time as medical director of the local Crippled Children's Services agency. You're never out of date as long as you have Google."

1958

George Spaeth

"When I arrived at HMS in 1954, I never expected to have a career in research. I was interested in clinical practice and still am, but since my year of research at the National Institutes of Health, I have not looked back. My major reason for writing now is to share news of two awards. In May 2010, I received the Mildred Weisenfeld Award for Excellence in Ophthalmology from the Association of Research in Vision and Ophthalmology. I was thrilled. To my added delight, in February 2011, I became the first recipient of the University of Geneva's A. Franceschetti Award."

1959

Boyd Burkhardt

"I retired from an extremely satisfying surgical career in 2006. The greatest advantage of plastic surgery is not financial, but rather avoidance of the MD–government insurance interface. My wife, Judi (a New England Deaconess Hospital RN), is now in an Alzheimer's care facility. HMS was the best experience of my life!"

Joan Wareham Flacke

"In April 2010, I had an aortic valve replacement in Tucson, where I had the wonderful support of Gary and his family. I recovered nicely. In July I got Barabas, a beautiful chestnut Peruvian horse. I rode him in a show in July in Denver and again in Fort Worth, Texas, in October. I spent Thanksgiving in Boston with Tim and had a wonderful time with his family, Eleanor, Owen, and Ruth, and wife, Melisa, who is interning in internal medicine. Tim is the head honcho of D2D.org. I spent Christmas in Tucson with Gary, Deanna, and little Alyssa. Chris has moved to Brooklyn, New York."

David Korn

"For more than two years I have been back in the omphalos as vice provost for research at Harvard University and an HMS professor of pathology. The vice provost position had not previously existed at Harvard, so setting up the program has been a rewarding enterprise for an 'HMS geezer' in his fifth career."

1962

Morton Goldberg

has been honored by the University of Illinois College of Medicine in Chicago with an endowed professorship in his name. Goldberg, who headed the Department of Ophthalmology at the University of Illinois from 1970 to 1989, is now a member of the ophthalmology faculty at the Wilmer Eye Institute at Johns Hopkins.

1963

John Mendelsohn

will step down as president of the University of Texas MD Anderson Cancer Center on August 31, 2011, to become co-director of its new Institute for Personalized Cancer Therapy.

1966

Dennis Bauman

"My daughter earned her RN last year and is completing a nurse practitioner program at Ohio State University. I have flunked retirement and am job hunting."

William Shipley

received the 2010 Jack Colbert Memorial Award from the Massachusetts Prostate Cancer Coalition. Shipley is the Andres Soriano Professor of Radiation Oncology at Massachusetts General Hospital.

1967

William Bernet

"My recent book, *Parental Alienation DSM-5 and ICD-11*, was published by Charles C. Thomas in 2010."

Larry Kadish

"Anna and I have been fully retired since June 2009. We

CLASS NOTES

NEWS FROM ALUMNI

moved to our 'weekend' home in Columbia County, New York, sold our Westchester home, and bought an apartment in Newton, Massachusetts, where our three children and seven grandchildren live. Anna is busy as a master gardener. I ran for the town council of Taghkanic, New York, and, after a contentious court battle over the legality of absentee ballots, won by four votes! Hence the nickname 'Landslide Larry.' We would welcome a visit from any classmates who are in the area."

1968

Jan Breslow

was awarded the American Heart Association's 2010 Research Achievement Award for "transcendent discoveries" of genes controlling cholesterol.

Jonathan Fielding

and JudyAnn Bigby '78 were appointed by President Barack Obama to the Advisory Group on Prevention, Health Promotion, and Integrative and Public Health.

Thomas Pollard

was one of 63 scientists worldwide elected to membership in the European Molecular Biology Organization in 2010. Pollard, the Sterling Professor of Molecular, Cellular, and Developmental Biology at Yale University, also received the Public Service Award from the American Society for Cell Biology.

1969

Elizabeth Anderson Mayer

"I retired from Kaiser Permanente in 2009 after a 35-year career. I enjoy retirement and continue to teach on a volunteer basis at the University of California, San Francisco."

1973

John Eichhorn and James Reinertsen

each received the 2010 John M. Eisenberg Patient Safety and Quality Award for Individual Achievement. Eichhorn, a professor of anesthesiology at the University of Kentucky, was recognized for developing and using practice standards and protocols that improved the quality of anesthesia care and patient safety. Reinertsen, head of the Reinertsen Group, a consulting firm in Alta, Wyoming, was recognized for his leadership in improving health care quality and safety in medical groups, hospitals, and health systems.

Steven Weinberger

"Janet and I remain in Philadelphia, where I've been working at the American College of Physicians, most recently as executive vice president and CEO. I recently completed a two-year stint as president of the Harvard Medical Alumni Association and continue to teach at HMS and the University of Pennsylvania."

1974

David Blumenthal

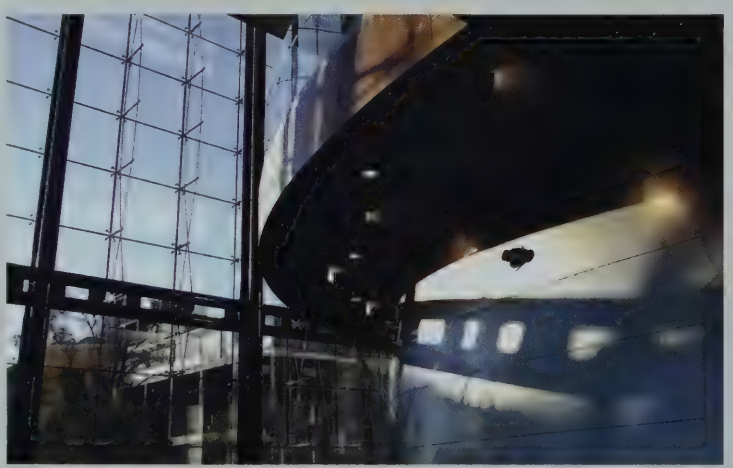
has stepped down as national coordinator for health information technology and has returned to HMS and Massachusetts General Hospital.

Albert Mulley

has been named director of the newly created Dartmouth Center for Health Care Delivery Science. Previously, Mulley served as an HMS associate professor of medicine and health policy and chief of the General Medicine Division and director of the Medical Practices Evaluation Center at Massachusetts General Hospital.

Patience White

received the Paulding Phelps Award from the American College of Rheumatology. White is a professor of medicine and pediatrics at the George Washington University School of Medicine and Health Sciences.



PHOTOS: JAN REISS

1976

Eliot Nierman

"I am still practicing and teaching general internal medicine at the University of Pennsylvania. I continue to enjoy photography and travel, with recent trips to destinations as varied as Acadia, Appalachia, Burma, Cambodia, Antarctica, and Patagonia. My daughter Jen is now on faculty in general internal medicine at NYU Bellevue, and my daughter Rachel works for JP Morgan."

1977

David Bell

"I have completed 25 years at the Centers for Disease Control and Prevention, where I work in the Division of Global HIV/AIDS. I travel to Africa to lead the CDC's efforts to prevent mother-to-infant HIV transmission. In December, I led the CDC's response to Haiti's cholera epidemic. My wife, Kathleen O'Toole, is a pediatric neuropsychologist and our children, Christine and Daniel, are students at Emory Medical School."

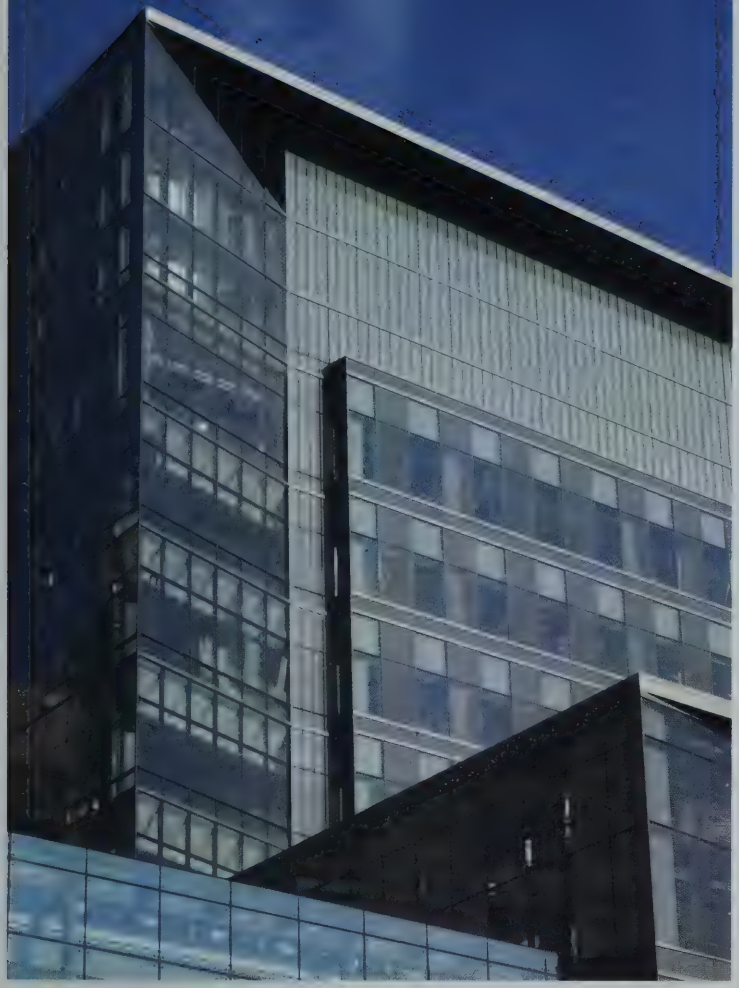
John Curnutte

has been appointed executive vice president of research and development at Portola Pharmaceuticals, Inc., in San Francisco.

1979

Chun-Wai Chan

has received the 2010 David Lawrence Community Service Award, which recognizes Kaiser Permanente employees and physicians who work to improve the quality of health worldwide.



1980

Steven Hyman
will step down as provost of Harvard University in June 2011 to return to research.

1982

Aaron Appiah
"I'm still practicing vitreoretinal surgery in Florida."

1983

Kevin Cullen
has been appointed by President Barack Obama to the National Cancer Advisory Board.

1984

Rox Anderson
completed a two-week medical mission to China and Vietnam, where he and his colleagues treated more than a hundred patients at the Vietnam Vascular Anomalies Center.

Nancy Andrews
received the 2010 Vanderbilt Prize in Biomedical Science, which honors accomplished women scientists who significantly contribute to the mentorship of other women in science. Andrews is dean of the Duke University School of Medicine, where she is also vice chancellor for academic affairs.

Daniel Berry
was recently named president of the Board of Directors of the American Academy of Orthopaedic Surgeons. He serves as chair of the Department of Orthopaedic Surgery at Mayo Clinic.

1986

Mitchell Katz
assumed the position of director of health services for Los Angeles County in January 2011.

1987

Cato Laurencin
has been elected to the National Academy of Engineering. Laurencin is dean of the University of Connecticut School of Medicine.

Raymond Price
recently coauthored *Global Surgery and Public Health: A New Paradigm*, which discusses surgery in the context of public health in developing countries.

1988

Anthony Monaco
has been named as the 13th president of Tufts University. He will leave a position as pro-vice-chancellor of planning and resources at the University of Oxford.

1990

Paul Farmer
has been named Harvard's first Kolokotrones University Professor of Global Health and Social Medicine. Farmer, who heads the HMS Department of Global Health and Social Medicine, cofounded Partners In Health.

1991

Daniel Murrey
is being honored with the Maribelle Connerat Award, given by Care Ring, a nonprofit health organization based in Charlotte, North Carolina.

1995

Michael Shlipak
has been promoted to professor of medicine at the University of California, San Francisco, where he is also the division chief for internal medicine.

2001

Raul Ruiz
was named senior associate dean for community engagement and partnerships at the University of California Riverside Medical School.

2002

Suzie Brown
released her debut album, *Side Streets*, this spring. In addition to pursuing a music career, Brown works part time as a cardiologist at the Albert Einstein Medical Center in Philadelphia.

2004

Jeremy Tucker
recently published *Before a Canyon*, a memoir about his time as a teacher for Teach for America.

2006

Brandon Lee
"I completed my residency in ophthalmology at the Doheny Eye Institute at the University of Southern California and am now completing a fellowship in medical retina at the Bascom Palmer Eye Institute in Miami, Florida."

Arlo Miller
has joined the dermatology department at Virginia Mason Medical Center in Seattle, Washington.

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

1938

William P. Boger, Jr.

Died July 24, 2010, at the age of 97, in Winchester, Massachusetts. Boger served on the editorial boards of several scientific journals, including *Clinical Medicine* and *Antibiotics and Chemotherapy*. He was also the editor-in-chief of *Chemotherapia*. He was predeceased by Mae, his wife of 34 years, and is survived by his sons, William Boger III '71 and Robert Boger '72; six grandchildren; and two great-grandchildren.

William N. Campbell, Jr.

Died December 20, 2010, at the age of 98, in Peoria, Illinois. Campbell opened a private family medicine practice in Peoria in 1941, continuing to make house calls until the day he retired in 1988. He was predeceased by his wife, Lillian, and son William. He is survived by his sons David, Donald, and Charles; his daughters, Deborah Millis and Pamela McGinty; eleven grandchildren; and eight great-grandchildren.

1939

James Locke Neller

Died December 31, 2010, at the age of 96, in Coronado, California. Neller served as a surgeon with the U.S. Navy in the Pacific Theater during World War II, achieving the rank of lieutenant. He practiced surgery in Los Angeles for 40 years, holding positions as chief of surgery and chief of staff at various hospitals before retiring in 1989. Neller was predeceased by his wife of 72 years, Patricia. He is survived by his daughters, Patricia Dear dorff, Shari Starrett, and Leigh Weesner; seven grandchildren; and eight great-grandchildren.

Russell E. Wigh

Died January 26, 2011, at the age of 96, in Columbus, Indiana. After working in the Civilian Conservation Corps, Wigh served in the U.S. Army Medical Corps in France during World War II, retiring as a lieutenant colonel. He joined the faculty of Columbia University College of Physicians and Surgeons in New York. In 1956, he was appointed professor and chair of radiology at the Medical College of Georgia in Augusta, where he served until 1963. Wigh went into private practice at Bartholomew County Hospital in Columbus, Indiana. He served as an associate clinical professor of radiology at the Indiana University School of Medicine. In 1976, he returned to the Medical College of Georgia, where he became emeritus professor of radiology in 1980, before returning to Columbus in 2004. Wigh was predeceased by his wife of 66 years, Emily, in 2006. He is survived by his sons, Russell and Richard; his daughter, Susan Faidley; seven grandchildren; and thirteen great-grandchildren.

1940

Samuel Potsubay

Died February 25, 2011, at the age of 95. Potsubay served as a major in the U.S. Army and was a chief medical officer in Canada's Northwest Territories during World War II. Following the war, he practiced internal medicine, specializing in cardiology, in Holyoke, Massachusetts, until his retirement in 1985. Potsubay was predeceased in 2002 by his wife of 62 years, Virginia. He is survived by his son, Richard; his daughters, Susie Symons and Laura Pucher; six grandchildren; and four great-grandchildren.

Thomas Ritzman

Died February 5, 2011, at the age of 97, in Chesapeake, Virginia. Ritzman was an officer in the U.S. Navy during World War II and served as a surgeon on the SS *Samaritan* in Tokyo Bay. After the war he established an obstetrics and gynecology practice in Concord, New Hampshire. Ritzman was a founding member of the Concord Clinic in 1958, now part of Dartmouth–Hitchcock Medical Center. He is survived by his wife of 20 years, Hannah; his sons, Thomas, Paul, and Jonathan Higgins; his daughters, Martha Johnson, Barbara Higgins, and Eleanor; eight grandchildren; and three great-grandchildren.

Hrad Zolmian

Died October 31, 2010, at the age of 96, in Carthage, North Carolina. During World War II, Zolmian served in the U.S. Army Medical Corps in the European Theater. In 1946, he established an internal and family medicine practice in the Blackstone Valley area of Rhode Island, and served as a staff physician at Memorial Hospital in Pawtucket, retiring in 1993. Zolmian was predeceased by his wife, Ruth, and his son, Rod. His nephew, Philip Kerrigan, survives him.

1941

Albert J. Finck

Died November 16, 2010. He was predeceased by his wife of 60 years, Ruth. Finck is survived by his son, David; his daughter, Harriet; and three grandchildren.

M. Laurens Rowe

Died December 30, 2010, at the age of 93. Rowe served as a surgeon in the U.S. Navy, rising to the rank of lieutenant in 1941. In 1943 he established an orthopedic surgery practice in Rochester, New York. Rowe served as an associate clinical professor in orthopaedic surgery at the University of Rochester School of Medicine and Dentistry, and, from 1956 to 1962, as the chief of orthopaedic surgery at Rochester General Hospital. Rowe was predeceased by his wife, Evelyn. He is survived by his sons, Stephen, Kevin, and James; nine grandchildren; and eight great-grandchildren.

Robert Weston, Jr.

Died March 9, 2010, at the age of 93. Weston joined the U.S. Army in 1944, serving as a medical internist in Germany, until he was discharged as a major in 1947. He settled in Milford, Connecticut, where he practiced family medicine and served as chief of staff at Milford Hospital, retiring at age 70. He is predeceased by his first wife, Eleanor, and second wife, Myrtie. He is survived by his four children, three stepchildren, seven grandchildren, and six great-grandchildren.

1943

Thomson Bryant, Jr.

Died March 1, 2011. Bryant served as a surgeon in the U.S. Army Medical Corps with the First Cavalry Division in the Pacific Theater during World War II. He later maintained a general

surgery practice in Lexington, Kentucky. He was also president of the Fayette County Medical Society and Central Baptist Hospital, both in Lexington. He was predeceased by his first wife, Dorothy, and his second wife, Betty. He is survived by his daughter, Patricia Malachowsky; three grandchildren; and three great-grandchildren.

George E. Deering

Died December 6, 2010, at the age of 93. Deering served as a captain in the U.S. Army Medical Corps during the Korean War. Upon his return in 1953, he became an assistant professor of psychiatry at the University of Massachusetts Medical School in Worcester, specializing in alcoholism and addiction. He retired in 1992. Deering was predeceased by his first wife, Ruby, in 1998. He is survived by his wife of 12 years, Shirley; his son, George; his daughters, Martha Deering-Hultgren and Rebecca Ballin; his stepsons, Robert Matson and Edward Matson; his stepdaughters, Patricia Regonini and Linda Matson; eleven grandchildren; and five great-grandchildren.

Eugene Francis Poutasse

Died November 30, 2010, at the age of 92, in Nellysford, Virginia. An officer in the U.S. Naval Reserve Medical Corps, Poutasse served with the U.S. Marine Corps on Guam during World War II. He joined the Department of Urology at the Cleveland Clinic Foundation in 1950, where he pioneered surgical treatments for renal arterial disease and associated hypertension. In 1961, he was corecipient of the Amory Prize of the American Academy of Arts and Sciences for his work in renal ischemia and hypertension. Poutasse practiced general, vascular, and reconstructive urology in Norfolk, Virginia, until 1983, when he moved to the Medical Society of Virginia Review Organization. He retired in 1994. Poutasse was predeceased by his daughter, Andrea Glenn. He is survived by Catherine, his wife of 49 years; his children Robert, Charles, Sarah Bent, Marc, Jacqueline, Alice Frazier, Sydney Gorby, and Frances Stacy; twenty-nine grandchildren; and ten great-grandchildren.

1944

James Robinson

Died February 25, 2011, at the age of 90, in Leesburg, Virginia. Robinson served in the U.S. Navy as a medical officer in World War II and the Korean War. Robinson practiced internal medicine at the Summit Medical Group and was an attending physician at Overlook Hospital in Summit, New Jersey, for 38 years. He is survived by his second wife, Rose-Joan Barron; his daughters, Carol King, Lynn Walsh, and Jan Hartt; his stepdaughter, Alice Barron; his stepson, Bruce Barron; six grandchildren; and eight great-grandchildren.

1945

William E. Johnson

Died August 30, 2010, at the age of 89, in Salem, Massachusetts. From 1946 to 1949 Johnson served as an assistant surgeon in the U.S. Navy, where he rose to the rank of lieutenant. In 1952, he founded Salem Orthopedic Surgeons, where he practiced orthopedic surgery until 1989. He also served as chief of orthopedics at Salem Hospital. Johnson is survived by his wife, Claire; his sons, David, Mark, Paul, and Robert; his daughters, Anne and Martha; eight grandchildren; and one great-grandchild.



PHOTO: COURTESY OF THE HOUGHTON LIBRARY, HARVARD UNIVERSITY

Mildred Jefferson 1926–2010

Mildred Jefferson '51, who died October 15, 2010, at the age of 84 in Cambridge, Massachusetts, had a career marked by firsts. From early childhood, she knew she wanted to be a doctor. At age five, she would tag along with a family physician on his rounds, peppering him with questions. One day she declared that she, too, wanted to be a doctor. The physician replied, "You go right on ahead."

That kind of early encouragement seems to have outweighed any obstacle Jefferson later encountered growing up in segregated East Texas. Considered gifted, she finished school at an accelerated pace and graduated from Texas College at the age of 18. Then she really began making history.

"I didn't know there were odds against what I was doing," she said. "I just made a list of three medical schools and applied." At the age of 20, Jefferson was admitted to Harvard Medical School, one of a handful of women in her class—and the first woman of color to be enrolled. Jefferson also became the first female surgeon of any race to graduate from the School.

Jefferson went on to become the first woman to intern in surgery at the former Boston City Hospital. She was later named an assistant clinical professor of surgery at the Boston University School of Medicine. Eventually she became the first woman elected to membership in the Boston Surgical Society.

Jefferson devoted many of her later years to political activism, channeling much of her energy into the fight against abortion. She was a founding member of Massachusetts Citizens for Life and a former president of the National Right to Life Committee.

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

1946

Henry W. Apfelbach

Died January 1, 2011, at the age of 89. Apfelbach served as a lieutenant in the U.S. Navy Medical Corps from 1947 to 1949, then moved to the University of Illinois at Chicago, where he taught orthopedic surgery. He held staff positions at several Chicago-area hospitals, including Northwestern Lake Forest Hospital and Advocate Good Shepherd Hospital, where he served as the first chief of staff. In 1968, Apfelbach founded Lake Forest Orthopaedics, which provided orthopedic surgical services to members of the Chicago Bears' football team for nearly two decades. Apfelbach is survived by his wife, Priscilla; his sons, Carl, Henry, and Peter; his daughter, Lura Lackie; his stepchildren, Margaret Stickel, Anan Raymond, Elizabeth Raymond, and Daniel Raymond; seventeen grandchildren; and two great-grandchildren.

Paul J. Fuzy, Jr.

Died October 19, 2010. Fuzy served in the U.S. Navy as a lieutenant junior grade and as chief medical officer aboard the USS *Roanoke* from 1950 to 1954. Following a brief tenure in Youngstown, Ohio, Fuzy set up practice in Fort Lauderdale, Florida, where he practiced as a colorectal surgeon for 40 years. Fuzy is survived by his wife of 46 years, Jetta; his sons, Chris and Paul; his daughter, Jeleen; and two grandsons.

Donald Harting

Died January 2, 2011, at the age of 88, in Exton, Pennsylvania, following a heart attack. Harting became a commissioned officer in the U.S. Public Health Service in 1946. Harting, who also earned a master's in public health at the Johns Hopkins University, served as the medical director for the Chicago region of the Children's Bureau, part of what is now the U.S. Department of Health and Human Services. In 1962, he helped establish the National Institute of Child Health and Human Development, an accomplishment that earned him the U.S. Public Health Service's Meritorious Service Medal in 1965. After retiring from the Public Health Service the following year, Harting continued in its service as a family planning consultant. In 1999, he co-founded the Delmarva Education Foundation in Salisbury, Maryland, where he served as the first executive director and, later, as a board member, until his death. Harting was predeceased by his first wife, Katherine, and second wife, Shirley. He is survived by his daughters, Jennifer Christian, Katherine, and Margaret Moore; his stepdaughter, Barbara Cole; his son, Donald; his stepsons, Donald Wheatley and Robert Wheatley; eighteen grandchildren and stepgrandchildren; and three great-grandchildren.

John M. Kinney

Died January 20, 2011, at the age of 89, in Sleepy Hollow, New York. Kinney served as an officer with the Naval Radiological Defense Laboratory in San Francisco from 1947 to 1949. He joined Harvard Medical School in 1958 as an instructor in surgery, then as an assistant professor of surgery, before moving, in 1963, to Columbia College of Physicians and Surgeons in New York City, where he rose to full professor. There Kinney helped found the Surgical Metabolism Unit at Columbia–Presbyterian Medical Center. Upon retirement in 1987, he became a visiting professor at the Rockefeller University, where he worked until 1999. In 1998, Kinney helped launch the journal *Current Opinion in Clinical Nutrition and Metabolic Care*, for which he served as an editor until 2008. Kinney authored and edited more than 400 articles and seven books on metabolism and nutrition. In 1987, the Nestlé Nutrition Institute and the Nutritional Sciences Education & Research Fund established the John M. Kinney Awards in his honor. Kinney was predeceased by his first wife, Joyce; his second wife, Mimi Scudder; and his son Paul. He is survived by his partner of thirteen years, Frances MacEachron; his son Walter; his daughter, Katherine Loving; his stepdaughter, Celine Hubler; his stepsons, Timothy Scudder and Kirby Scudder; and seven grandchildren.

George D. Penick

Died January 4, 2011, at the age of 88, in Southern Pines, North Carolina. Penick served as a captain in the U.S. Army. In 1949, he joined the University of North Carolina's Department of Pathology as an instructor, researching hemorrhage and thrombosis, and became a professor in 1963. In 1970, Penick became the chair of pathology at the University of Iowa Carver College of Medicine, where he worked until his retirement. To honor his work, the department established the George D. Penick Award for Excellence in Education. Penick was predeceased by his wife, Marguerite, and his son Anderson. He is survived by sons George, Jr., Hal, and David; his daughter, Marguerite Parks; nine grandchildren; and two great-grandchildren.

1947

Harrison O'Connor

Died on December 28, 2010, at the age of 86, in Milford, Massachusetts, of complications from pneumonia. O'Connor had finished his residency at Children's Hospital Boston when he contracted polio and had to be placed in an iron lung for several months. When he recovered, O'Connor completed training as a pediatric orthopedic surgeon and, later, as a psychiatrist. For more than 50 years, O'Connor maintained practices in both disciplines in Massachusetts. He is survived by his wife, Elizabeth; his stepchildren, Donna Wick, Dwyer Vessey, Lynne Glode, Jeffrey Leahy, and Janet Phillips; and ten stepgrandchildren.

1948

Donald Charles Fyler

Died February 4, 2011, in Wellesley, Massachusetts. Fyler served in the U.S. Navy during World War II. After the war, he founded the pediatric cardiology department at the Children's Hospital Los Angeles and was a professor of pediatrics at the University of Southern California in Los Angeles. He was later a professor of pediatrics at HMS and associate chief of cardiology at Children's Hospital Boston, where he initiated the New England Regional Infant Cardiac Program. Fyler coauthored a textbook on pediatric cardiology. His wife, Carol, predeceased him in 2009. Fyler is survived by five children,

eight grandchildren, and a great-grandchild.

William S. Kiyasu

Died November 2, 2010, at home, in Sacramento, California, after a two-year battle with cancer. After serving as a lieutenant commander in the U.S. Navy Medical Corps, Kiyasu joined his father and brother's medical practice where he remained until his retirement in 2002. In 1953, Kiyasu received the first National Institutes of Health Fellowship in Pediatric Hematology. In addition to his private practice, he taught and served as vice-chairman of the Department of Pediatrics at Children's Hospital in San Francisco. Kiyasu was also a clinical professor of pediatric medicine and, eventually, professor emeritus at the University of California, San Francisco. He served as the chief pediatrics advisor to Shriners Hospital in San Francisco until moving to Sacramento. He is survived by his wife of 51 years, Kikue; his daughters, Miriam and Emily; his sons, Crawford and Charles; and three grandchildren.

W. William Nagle

Died September 30, 2010, at the age of 86, in Paoli, Pennsylvania. Nagle opened his first radiology office in 1959 in Media, Pennsylvania, and later practiced in Philadelphia and Bryn Mawr. He was predeceased by his children, Wynn and Doug, and a stepdaughter, Sandy Gachot. He is survived by his wife, Laila; his stepsons, Chip Gachot, Brad Gachot, and Chris Gachot; his stepdaughter Laila Gachot Adams; and eight grandchildren.

David W. Parsons

Died on August 5, 2010, at the age of 86. Parsons was a lieutenant in the U.S. Navy. He practiced internal medicine and allergy in Wayland and in Concord, Massachusetts, for 40 years, and he was on the staff of Emerson Hospital in Concord. Parsons is survived by his wife of 60 years, Mary; his sons, Preston and David; his daughter, Sarah Thacher; and five grandchildren.

1949

James Edwin Wood III

Died August 15, 2010, at the age of 85, in Bryn Mawr, Pennsylvania. Wood served in the U.S. Navy's V-12 program. During the Korean War, he was a captain and a flight surgeon at the U.S. Air Force School of Medicine, where he received the Air Force Commendation Ribbon. In 1958, Wood joined the Medical College of Georgia as director of the Georgia Heart Association Laboratories for Cardiovascular Research. While there, he published extensively on vascular disease and wrote *The Veins*, which was published in 1965. In addition, Wood was the Virginia Heart Association Research Professor of Cardiovascular Research at the University of Virginia School of Medicine, where he also held posts as acting chairman of the Department of Physiology, associate dean of the School of Medicine, and acting dean of medicine. He later became a professor of medicine at the University of Pennsylvania School of Medicine and chairman of medicine at the Pennsylvania Hospital in Philadelphia, positions he held for 21 years before retiring as emeritus professor in 1990. Wood established the J. Edwin Wood Clinic, a nonprofit medical and surgical facility. He was president of the Southern Section of the American Federation for Clinical Research, the American Clinical and Climatological Association, and the American Heart Association's Southeastern Pennsylvania Chapter and Health Promotion Council. He is survived by his wife of 62 years, Ann; his sons, Edwin and James; his daughters, Emily Starkey and Ann Gregg; eleven grandchildren; and two great-grandchildren.

1950

William F. McNeely

Died January 2, 2011, at the age of 83, from complications of Alzheimer's disease, lymphoma, and pneumonia. He served as a pharmacist's mate in the U.S. Navy from 1945 to 1946. McNeely joined the medical staff at Massachusetts General Hospital in 1957, where he remained for 50 years. He established a private practice in internal medicine and, in 1969, became an HMS clinical instructor in medicine. After retiring from his practice in 1997, he continued to work on Mass General's clinicopathological conferences until around 2002. McNeely was predeceased by his wife, Betty, in 1995. He is survived by his stepdaughter, Sarah Weinberg, and several nieces and nephews.

Avard M. Mitchell

Died on February 23, 2011, at the age of 91, in Wellesley, Massachusetts, from complications of a stroke and Parkinson's disease. Mitchell, who also held a doctorate in chemistry, served in the U.S. Army from 1944 to 1946, under assignment to the Manhattan Project. In 1954 he settled in Wellesley, where he practiced internal and family medicine for 36 years. His son Eric predeceased him in 1998. He is survived by his wife of 57 years, Marjorie; his daughter, Susan Lewis; his sons Mark, Dean, and David; and three grandchildren.

1952

John E. Lindley

Died January 27, 2011, at the age of 84, in Marion, Mississippi. Lindley served two years in the U.S. Navy during World War II, rising to the post of pharmacist mate second class. Lindley held several subsequent positions, including assistant instructor in obstetrics and gynecology at Baylor University in Waco, Texas; clinical instructor in obstetrics and gynecology at the University of Mississippi Medical Center; and chief of the Department of Obstetrics and Gynecology and chief of staff at Anderson Regional Medical Center, in Meridian, Mississippi. He helped found and for 17 years served as president of the Board of Directors of Meridian's Jefferson Davis Academy, and he helped incorporate Marion, Mississippi, before serving as its first mayor. Lindley held 17 patents on inventions, including the Lindley I and II newborn resuscitators. He was past president of the East Mississippi Medical Society, the University of Mississippi Ob/Gyn Alumni Association, and the East Mississippi Medical Society. Lindley is survived by his wife, Marie; his daughter, Lisa McCleskey; and his sons, John, Jr., and Mark.

Peter Teel

Died January 22, 2011, at the age of 83, in Boston, Massachusetts.

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

Teel served as a medical officer in the U.S. Navy aboard the aircraft carrier USS *Essex* in the western Pacific until 1956. Following his military service, Teel established a surgical practice in Billings, Montana, maintaining it until his retirement in 1990. Teel was predeceased by his daughter, Elizabeth. He is survived by his wife of 58 years, Katherine; his sons, Derrick and Philip; and five grandchildren.

1953

David Henry Gray

Died December 25, 2010, at the age of 83. In 1957, Gray founded the Ledgemere Morgan Horse Farm in Shelburne, Vermont. As a member of the Vermont Department of Health, Gray helped establish that state's ambulance service and took charge of its nursing homes. He is survived by his wife, Dorothy; his daughters, Nancy, Carol, Susan, and Sara; and seven grandchildren.

John B. Sacci

Died February 14, 2011, at the age of 84, in Mt. Kisco, New York. He served in the U.S. Army during World War II as a lieutenant. Sacci joined the Mount Kisco Medical Group in 1959, where he practiced for more than 35 years. Sacci is survived by his wife, Louise; his daughter, Constance Fitzgerald; his sons, John, Jr., and Thomas; and seven grandchildren.

James Zachary

Died February 15, 2011, at the age of 83, of cancer. Zachary practiced medicine at Baltimore City Hospital, now Johns Hopkins Bayview Medical Center, for nearly 50 years, except for four years in the U.S. Air Force. He joined the Johns Hopkins University School of Medicine faculty in 1963 and founded Bayview's renal medicine division in 1974. Zachary served as a chairman and board member of the National Kidney Foundation of Maryland. In 1978, he was named chairman of the Kidney Commission of Maryland, and in 1997, the Kidney Foundation recognized his lifetime contributions to renal medicine. Zachary retired around 2001, but continued to see patients and to serve as an associate professor at Johns Hopkins until around 2008. He is survived by his wife of 55 years, Annelies Sondheim, and his son, Peter.

1954

John Farnam Bowen

Died September 17, 2010, at the age of 84. Bowen served on the USS *Strickland* destroyer escort at the end of World War II and spent a year on the tuberculosis service at the State University of New York Upstate Medical Center. In 1960, Bowen moved to Canandaigua, New York, where he began a practice in internal medicine, later joining the Canandaigua Medical Group. Bowen also was a member of the Board of Directors and the chief of staff at F. F. Thompson Hospital in Canandaigua. Following his retirement from the Canandaigua Medical Group, he became medical director of the Ontario–Yates Hospice in Geneva, New York. Bowen was predeceased by his first wife, Ruth, and his second wife, Martha. He is survived by his sons, John, Eliot, and David; his stepsons, Dan Vorenberg, Tom Vorenberg, and Michael Vorenberg; five grandchildren; and five stepgranddaughters.

1956

Lawrence Baker

Died September 20, 2010. Baker served as a captain in the U.S. Army from 1957 to 1959 before being appointed as an HMS clinical instructor in medicine and as an associate in medicine at the former Beth Israel Hospital. He worked with the Massachusetts Academy of Trial Lawyers and the Massachusetts Bar Association on medical and legal issues. He was past treasurer of the HMS Class of 1956. He is survived by his wife of 54 years, Phyllis; his son, Jonathan; his daughters, Elissa Gittes and Elizabeth Jacobi; and six grandchildren.

M. Michael Eisenberg

Died February 24, 2011, at the age of 80, in Manhattan, New York. For nearly 20 years, Eisenberg served as a professor of surgery at Weill Cornell Medical College. As director of its Surgical Education Program, he trained generations of medical students, and was selected five times by his students to receive a graduation teaching award. He is survived by his wife of 27 years, Barbara Yetka-Eisenberg; his daughters from his first marriage to Carol Kossin Cleveland, Elyse, Ellen, and Andrea Michaels; and two grandchildren.

A. David Goodman

Died January 12, 2011, at the age of 78. Goodman joined the faculty of Albany Medical College in 1964 as chief of the Division of Endocrinology, a position he held until shortly before his retirement in 1996. He was the recipient of several clinical and teaching awards, including the Pillars Award of Albany Medical Center. The Goodman Diabetes Service at Albany Medical Center was named in his honor, as was the annual Goodman Diabetes Symposium. He is survived by his wife, Charlotte; his daughter, Andrea Hansell; his sons, Matthew and Jeffrey; and five grandchildren.

Thomas Edward Moore, Jr.

Died December 29, 2010, at the age of 79, from cancer. Moore served two years in the U.S. Navy Reserve as a flight surgeon. Following a year in London as a Fulbright Scholar in ophthalmology, he was appointed in 1964 as a clinical professor of ophthalmology at the University of California, San Francisco; he was later named a clinical professor emeritus. He worked in San Francisco, combining research and private practice, for 40 years. Moore is survived by his companion, Ingrid Gillette; his sons, Thomas and Nicholas; his daughters, Lennie Gotcher, Katharine, and Valerie Ramler; and twelve grandchildren.

1957

L. F. "Fritz" Fenster

Died January 19, 2011, at the age of 79, in Seattle, Washington. Following a fellowship in liver disease at Grace–New Haven Hospital in Connecticut, Fenster moved to Seattle, Washington, to take a post as chief medical resident at King County Hospital and the University of Washington in Seattle. After a two-year term as a clinical associate at the National Institutes of Health, Fenster returned to Seattle as section head of the Division of Gastroenterology at King Coun-

ty Hospital. In 1967, he joined Seattle's Virginia Mason Medical Center, where, over a 20-year period, he served as medical director of the Office of Value Assessment, associate chairman of the Quality Assessment Committee, and head of the hepatology subsection. Fenster also served for 18 years as a clinical professor of medicine at the University of Washington, retiring in 1993. In 1997, he returned to the university as a clinical professor in the Department of Health Services. Fenster received many awards, including the R.H. Williams Superior Leadership in Medicine Award from the Seattle Academy of Internal Medicine in 1991, the James Tate Mason Award from the Virginia Mason Medical Center in 1995, the annual distinguished clinician award from the American Gastroenterological Association in 1997, and several best teacher awards. He is survived by his niece, Lisa Walters Girard.

Prentiss Dettman

Died February 7, 2011, at the age of 77. Dettman served in the U.S. Navy at the National Naval Medical Center in Bethesda, Maryland, and continued in the Navy Reserves for one year, achieving the rank of lieutenant commander. He joined Case Western Reserve University School of Medicine as an assistant professor of radiology in 1967, becoming an associate professor in 1971. In 1972, at the University of Nebraska Medical Center in Omaha, he was appointed the Eppley Foundation Professor of Radiation Therapy. In 1978 he joined a private practice and continued teaching at the University of Nebraska as a visiting professor until his retirement in 1990. Dettman is survived by his wife of 55 years, Evelyn Hollingsworth; his daughter, Cindy; his sons, David and Brian; four grandchildren; and a great-granddaughter.

1959

Charles J. Epstein

Died February 15, 2011, at the age of 77, at his home in Tiburon, California, of pancreatic cancer. Epstein joined the faculty of the University of California, San Francisco in 1967 as the chair of the medical genetics division. He became a professor of biochemistry and pediatrics in 1972 and was named director of UCSF's human genetics program in 1997. In 1993, he survived serious injuries after opening a piece of mail sent by the Unabomber, Theodore Kaczynski. Epstein served as president of the American College of Medical Genetics and the American Society of Human Genetics, both of which presented him with lifetime achievement awards. He also served as president of the American Board of Medical Genetics. Most recently, Epstein chaired both the Scientific Advisory Board and Board of Trustees of the Buck Institute for Research on Aging, which established an annual lecture series in his name. A leading researcher, educator and clinician in genetics, Epstein treated thousands of patients and trained hundreds of doctors, scientists, and genetic counselors. He published more than 500 scholarly papers and authored and edited several books. Epstein is survived by his wife and HMS classmate, Lois; his sons, David, Jonathan, and Paul; his daughter, Joanna; and six grandchildren.

1964

David Ward Havens

Died February 28, 2011, at the age of 72, in Springfield, Tennessee. Havens served as a captain in the U.S. Air Force at March Air Force Base near Riverside, California, from 1968 to 1970. He maintained private psychiatric practices in Boston from 1970 to 1992 and in Hendersonville and Springfield, Tennessee, from 1992 to 2007. Havens authored *A Heart Is Healed*, a book of reflections on the nature of loss, grief, and healing. He is survived by his wife of 48 years, Sarah; his sons, Andrew and John; and three grandchildren.

1966

Melvin David Levine

Died February 17, 2011, at the age of 71, in Rougemont, North Carolina. Levine served in the U.S. Air Force and received the Meritorious Service Award. For 14 years he was chief of the Division of Ambulatory Pediatrics at Children's Hospital Boston. He also served as an HMS associate professor of pediatrics. In 1985, he joined the faculty of the University of North Carolina at Chapel Hill, where he became the Thomas E. Castelloe, M.D. Distinguished Professor in Developmental Behavior Pediatrics and founded the Clinical Center for Study of Development and Learning, serving as its director until 2007. Levine is survived by his wife of 42 years, Barbara Ann (Bambi) Mitchell.

1974

Howard D. Kirshenbaum

Died May 26, 2010, at the age of 61, in Boston, of cancer. Kirshenbaum was an assistant professor of cardiology at the University of Massachusetts Medical School in Worcester; practiced cardiology with the Charles River Medical Associates in Marlborough, Massachusetts; and, for ten years, served as director of medical affairs at Marlborough Hospital. Kirshenbaum also trained cardiology fellows at Brigham and Women's Hospital. For that work he was posthumously honored with the Eugene Braunwald Teaching Award. Kirshenbaum is survived by his wife of 36 years, Elaine; his son, Daniel; his daughter, Jennifer; and his mother, Lucy.

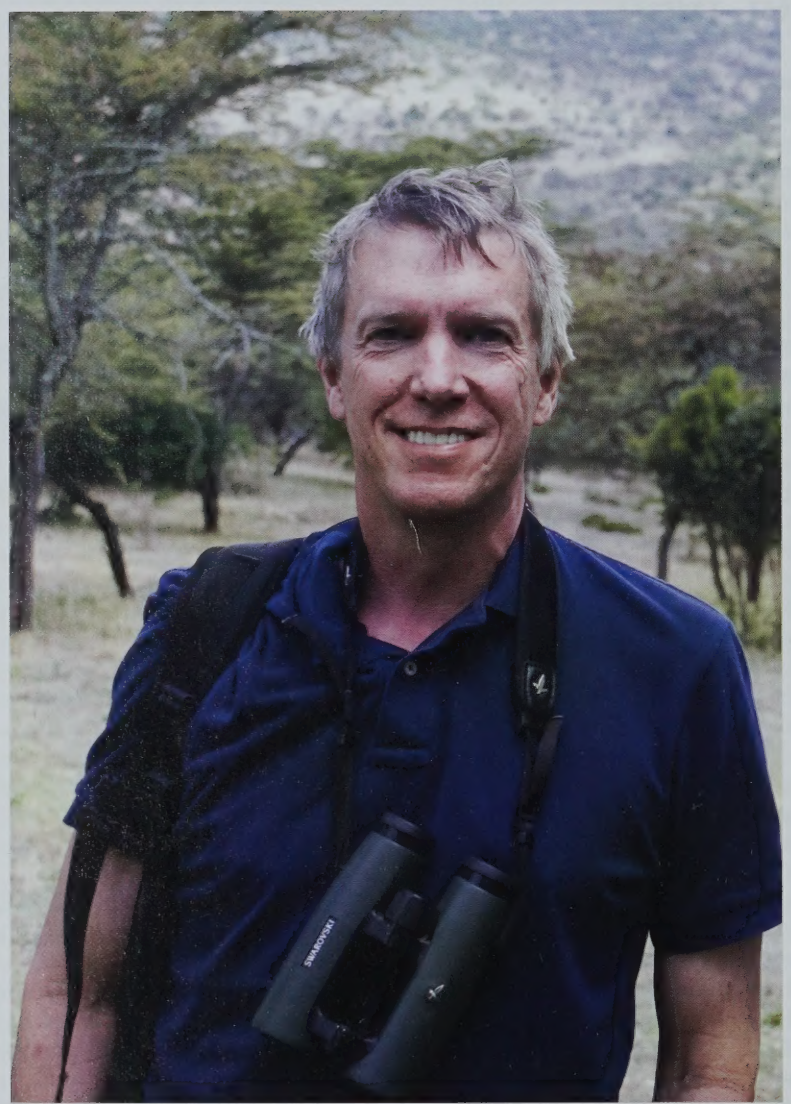
2005

Gregory Aaron Feldman

Died November 15, 2010, at the age of 33, in Chicago, Illinois. In 2007, during his residency at Stanford Medical Center, Feldman received the Arnold P. Gold Foundation Humanism and Excellence in Teaching Award; the following year he earned the center's General Surgery Resident Teaching Award, its Vascular Surgery Resident Award, and its Emergency Medicine Residents' Consultant of the Year Award. In 2009, he was appointed the center's chief surgical resident. In 2010, Feldman volunteered as a surgeon in Rwanda with Medical Missions for Children. In July 2010, following completion of his general surgery residency, Feldman began a fellowship in vascular surgery at Northwestern University. Feldman is survived by his parents, Rhoda and Sidney; his brother, Howard; his sister, Judith; and three nieces.

TAKING A HISTORY

PROFILE OF MARK STOECKLE



With high schoolers from New York's Trinity School, Stoeckle analyzed 217 items, uncovering DNA from bison in dog biscuits, ostrich in duster feathers, and giant flying squid in a popular East Asian snack.

CLAIMS TO FAME: Adjunct Faculty Member, Program for the Human Environment, The Rockefeller University; Clinical Associate Professor of Medicine, Department of Medicine, Weill Cornell Medical College; Scientific Advisor, International Barcode of Life Project

WINGED FANCY: "The natural world has always been an interest of mine," says Mark Stoeckle '78. "I collected butterflies when I was little, then I got interested in birds." Birdwatching expeditions with the Massachusetts Audubon Society made way for new pursuits: medical school, then molecular biology research. But Stoeckle's recreational and academic interests melded in 2003 when he became involved with both the All Birds Barcoding Initiative, which seeks to genetically characterize the roughly 10,000 known species of birds worldwide, and the International Barcode of Life Project.

A SINGLE ADDRESS: The International Barcode of Life Project aims to gather standardized genetic data on all Earth's plant and animal species—or at least on the roughly two million named species—and to file them as DNA barcodes in an open-access electronic library. "With barcoding," Stoeckle says, "it doesn't matter what the sample is, you analyze the same gene segment." For animals, that segment is a short genetic marker in mitochondrial DNA.

SOMETHING FISHY: Having DNA identifications on hundreds of thousands of animals can help efforts to preserve the planet's biodiversity, Stoeckle says. The U.S. Food and Drug Administration, for instance, uses the project's DNA barcoding method to identify marketplace fraud in fish and shellfish products. Proof of the method's value was illustrated in a high school students' barcoding project that Stoeckle led. Dubbed Sushigate, this project revealed that fish in sushi purchased from randomly selected restaurants and markets was mislabeled nearly one-quarter of the time. The results, which wound up on page one of *The New York Times*, have implications for environmental health, says Stoeckle. "Fish being sold might be from an endangered species. Once it's cut up, though, no one knows what it is." DNAHouse, another Stoeckle-led project, highlighted species pervasiveness in food and other consumer products. With high schoolers from New York's Trinity School, Stoeckle analyzed 217 items, uncovering DNA from bison in dog biscuits, ostrich in duster feathers, and giant flying squid in a popular East Asian snack. Overall, the team identified DNA from 95 animal species—and possibly a new species of cockroach.

IT'S SCIENCE!: Stoeckle's collaborations with students keep him in touch with his youthful naturalist leanings. "The students are thrilled to be using DNA analysis to make discoveries about our environment," he says. "It's learning science by doing science."

—Ann Marie Menting

PHOTO: COURTESY OF MARK STOECKLE



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